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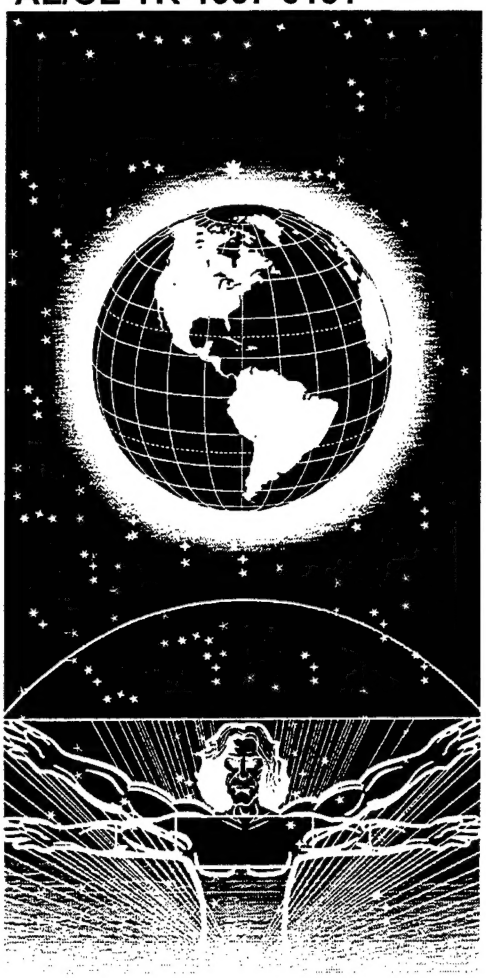

UNITED STATES AIR FORCE RESEARCH LABORATORY

CHROMIUM ENVIRONMENTAL RISK ASSESSMENT

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FOR THE DIRECTOR

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A review of chromium environmental criteria, supporting scientific studies and recent research activities was conducted to determine the implications of evolving observations on cancer risk to DoD environmental clean-up programs. Public concern over the occupational cancer risk of hexivalent chromium is influencing a new assessment of the risk data. Toxicology literature on the human health hazards, cancer and non-cancer, was reviewed. On-going epidemiology efforts were unavailable for a thorough assessment. Data gaps in the literature were noted as support for research recommendations. Alternatives to chromium speciation at environmental clean-up sites were recommended as an interim measure. An extensive bibliography is provided.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

This effort was performed by Operational Technologies Corporation (OpTech). Activities were conducted under the Project Management of Mr. Erik Vermulen, 1010 Woodman Drive, Suite 160, Dayton OH 45432. The work was completed under U.S. Air Force Contract F41624-94-D-9003/004 between April 1996 and October 1997. Lt Col Terry Childress, Director of the Armstrong Laboratory Occupational and Environmental Health Directorate Toxicology Division (AL/OET), served as contract monitor. The government program manager was Lt Col Larcom of AL/OET.

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LIST OF ABBREVIATIONS AND ACRONYMS

µg	microgram
ACGIH	American Conference of Governmental Industrial Hygienists
ARAR	Applicable or Relevant and Appropriate Requirement
ATSDR	Agency for Toxic Substance and Disease Registry
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act
Cr	chromium
Cr(III)	chromium(III), trivalent chromium
Cr(VI)	chromium(VI), hexavalent chromium
CrO_3	chromium(VI) oxide
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DoD	Department of Defense
DOE	Department Of Energy
DPX	DNA-protein cross-links
E. coli	*Escherichia coli*
EPA	Environmental Protection Agency
g	gram
IARC	International Agency for Research on Cancer
IDLH	Immediately Dangerous to Life and Health
IRIS	Integrated Risk Information System
IRPIMS	Installation Restoration Program Information Management System
JHU	Johns Hopkins University
kg	kilogram
l	liter
lb.	pound
LOEL	lowest observed effect level
m^3	cubic meter
MAK	Federal Republic of Germany Maximum Concentration Values
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
mg	milligram
mg	milligram
ml	milliliter
NIOSH	National Institute For Occupational Safety and Health
NMRI/TD	Naval Medical Research Institute Toxicology Detachment
NOAEL	no observed adverse effect limit
NPL	National Priority List
NTP	National Toxicology Program
OCAW	Oil, Chemical and Atomic Workers International Union
OSHA	Occupational Safety and Health Administration
PEL	Permissible Exposure Limit
ppm	parts per million
RBC	red blood cell
RCRA	Resource Conservation and Recovery Act
RfC	Reference Concentration
RfD	Reference Dose
SARA	Superfund Amendments and Reauthorization Act
SDWA	Safe Drinking Water Act
TLV	Threshold Limit Value
TRI	Toxic chemicals Release Inventory
WBC	white blood cell

CHROMIUM ENVIRONMENTAL RISK ASSESSMENT

INTRODUCTION AND REQUIREMENTS

Chromium is an element found in soil. It normally exists in three major valence states: chromium(0), chromium(III) and chromium(VI). Chromium(III) occurs naturally in the environment while chromium(VI) and chromium(0) are generally produced by industrial processes. Chromium also has the potential of forming complexes in a variety of transient stages.

Exposure to chromium in small amounts results from breathing air or ingesting drinking water and food containing chromium. Much higher exposure to chromium occurs to people working in certain chromium industries (occupational exposure) and to people who smoke cigarettes.

The three forms of chromium differ in their effects on health. Chromium(0) is the least common and is not well characterized in terms of levels of exposure or potential health effects. Chromium is considered to be an essential nutrient to the human body that helps to maintain normal metabolism of glucose, cholesterol and fat in humans. Chromium(III) is thought to be the essential food nutrient form of chromium. Trivalent chromium (Cr(III)) in very large doses may be harmful. Most adverse health effects are caused by the third form of chromium, hexavalent chromium (Cr(VI)). Chromium(VI) is an irritant and short-term, high-level exposure can result in adverse effects at the site of contact, such as ulcers of the skin, irritation of the nasal mucosa, perforation of the nasal septum and irritation of the gastrointestinal tract. Chromium(VI) may also cause adverse effects in the kidney and liver.

Current Criteria and Applicable or Relevant and Appropriate Requirements

Hexavalent chromium is currently regulated by the Occupational Safety and Health Administration (OSHA) and the Environmental Protection Agency (EPA). Other forms of chromium, such as soluble chromic salts, insoluble salts or chromium metal are also regulated. The National Institute for Occupational Safety and Health (NIOSH) has recommended more stringent standards for occupational exposure to chromic acid, chromium(VI) compounds as well as any noncarcinogenic or carcinogenic forms of chromium. Current regulatory standards are summarized in Table 1. The cancer ratings by several agencies are summarized in Table 2. Other regulatory standards vary by state or local government (e.g., Safe Drinking Water Act (SDWA), Clean Air Act, Clean Water Act (CWA)).

Under the provisions of the Comprehensive Environmental Response, Compensation and Liability Act of 1980 (CERCLA), any federally promulgated environmental standard affecting air, water or soil cleanup will be accepted at sites requiring cleanup under CERCLA as an applicable or relevant and appropriate requirement (ARAR). Standards applicable as ARARs for CERCLA sites include, but are not limited to, those promulgated under the following: SDWA, Resource Conservation and Recovery Act (RCRA), CWA, OSHA. Therefore, any revision to a chromium standard, whether occupational or otherwise, will cause CERCLA sites to consider

the standard as an ARAR for cleanup to the sites. The Department of Defense (DoD) is responsible under CERCLA for cleanup of past contaminated sites.

TABLE 1: SOME CURRENT REGULATORY STANDARDS

Regulation	Cr(III) as Cr & chromium metal	Cr(VI) water-soluble compounds	Cr(VI) insoluble compounds
OSHA PELs	0.5 mg/m^3 1.0 mg/m^3		
OSHA Ceiling		0.1 mg/m^3 (CrO_3)	0.1 mg/m^3 (CrO_3)
ACGIH TLVs	0.5 mg/m^3 0.5 mg/m^3	0.05 mg/m^3	0.05 mg/m^3
IDLH		30 mg/ m^3 (CrO_3)	
RCRA Action Level (Total Cr(VI))		Air 0.00009 $\mu g/m^3$ Water 1 mg/l Soil 400 mg/kg	Air 0.00009 $\mu g/m^3$ Water 1 mg/l Soil 400 mg/kg
SDWA (Total Cr)		MCL & MCLG = 0.1 mg/l	
SDWA (Cr(VI))		MCL = 0.05 mg/l	MCL = 0.05 mg/l
SARA Title III	Report CERCLA or 5000 lb. total Cr		

Notes:
PEL = Permissible Exposure Limit (8 Hour Average)
Ceiling = One Time Maximum Exposure Level
ACGIH = American Conference of Governmental Industrial Hygienists
TLV = Threshold Limit Value (8 Hour Average)
IDLH = Immediately Dangerous to Life and Health (Cancer)
RCRA = Resource Conservation and Recovery Act; Action levels trigger further investigation or remediation
SDWA = Safe Drinking Water Act; States may promulgate a lower limit
MCL = Maximum Contaminant Level
MCLG = Maximum Contaminant Level Goal
SARA Title III = Title III of the Superfund Amendments and Reauthorization Act of 1986 and Title III of the Clean Air Act Amendments of 1990; Reportable quantity in air

TABLE 2: CURRENT CANCER RATINGS*

	NIOSH	MAK	IARC	EPA	NTP	TLV
Cr(II)						
Cr(III) as Cr		A2	3			A4
Cr metal			3			A4
Cr(VI) soluble	X	A2	1	A	1	A1
Cr(VI) insoluble	X		1	A	1	A1

Notes: NIOSH
X = Carcinogen defined with no further categorization
MAK = Federal Republic of Germany Maximum Concentration Values in the Workplace
A2: Unmistakably carcinogenic in animal experimentation only
B: Justifiably suspected of having carcinogenic potential
IARC = International Agency for Research on Cancer
1: Carcinogenic to Humans, sufficient evidence of carcinogenicity
3: Not classifiable as to carcinogenicity to humans
EPA = Environmental Protection Agency (Prior to Draft Revised May 96)
A: Human carcinogen, sufficient evidence from epidemiological studies to support a causal association between exposure and cancer
NTP = National Toxicology Program
1: Known to be carcinogenic, sufficient evidence from human studies
TLV = ACGIH Cancer Rating
A1: Confirmed human carcinogen
A4: Not classifiable as a human carcinogen
* ACGIH, 1993.

Revision Drivers

A driving force behind the proposed revision of the chromium standard is a consumer advocacy group concerned over chromium toxicity. The Public Citizen Health Research Group and the Oil, Chemical & Atomic Workers International Union (OCAW) petitioned OSHA in 1993 for an Emergency Temporary Standard to lower the amount of exposure to chromium(VI) compounds in the workplace to 1/200th of current allowable levels. The consumer advocacy group and labor union cite studies showing that chromium(VI) compounds, commonly used in many industrial processes, have the potential to cause lung cancer in up to 22% of workers who are exposed for a working lifetime to levels currently allowed by OSHA. Dr. Sidney M. Wolfe, MD, Director of the Public Citizen Health Research Group, stated that "the data make clear that current permissible exposure levels do not do enough to protect worker's health and must be changed" (Public Citizen's Health Research Group and the Oil, Chemical and Atomic Workers International Union, 1993).

A report prepared for OSHA by the KS Crump Division of the ICF Kaiser Corporation titled "Evaluation of Epidemiological Data and Risk Assessment for Hexavalent Chromium" supports

the carcinogenicity of hexavalent chromium with six sets of epidemiological data. The epidemiological data allow estimation of the values for the input variables used in quantitative risk assessment, namely, levels of exposure and duration of exposure (or cumulative exposure), observed number of cancer deaths by exposure category and expected numbers of cancer deaths by exposure category. Some of the data were not tested for statistically significant tendencies. Other studies did not speciate total chromium. The other data gap from these studies was the significance of smoking on the estimated increased lung cancers (ICF Kaiser, 1995).

The John Hopkins University review of the carcinogenicity of hexavalent chromium addresses the concerns over the past epidemiological data and risk assessment for hexavalent chromium. Dr. Lees of the John Hopkins University recently reviewed the cancer risk associated with hexavalent chromium. The study included 2357 personnel of which 120 died from lung cancers. The study specified smoking data for 57% of the personnel studied. Dr. Lees also speciated chromium(VI) from other forms of chromium. This study supports an occupational exposure limit set at 0.275 $\mu g/m^3$ over an 8-hour workday to protect to the 1/1000 excess cancer risk level (Lees *et al.*, 1996; Gibb *et al.*, 1996a and 1996b). The impact of this study will be further addressed in this report.

Impact on Department of Defense

DoD will be impacted in both the occupational as well as the environmental enforcement of regulations. The DoD maintains hundreds of bases which operate major weapons systems. The DoD also is responsible for many National Priority List (NPL) sites under CERCLA and must enforce all chromium standards to ensure that the public safety and health is maintained in any cleanup operation. The Navy/Industry Task Group prepared a report in October 1995 titled "Impact of Anticipated OSHA Hexavalent Chromium Worker Exposure Standard on Navy Manufacturing and Repair Operations". This report outlined the impact of the occupational chromium standard revision on Naval industrial operations (e.g., welding, painting, depainting) (See Table 3). The report did not include any impact to DoD or Navy in the cleanup of CERCLA sites (Navy/Industry Task Group, 1995). There are 153 federal facilities which are on the NPL list. Of these 153, it is estimated that 33% contain chromium contamination (ATSDR, 1993).

The impact to the DoD from the proposed change to the chromium standard is immeasurably large. The mission of the DoD is National Defense. The DoD acquires, maintains and disposes raw materials in the form of weapons systems, communications equipment, services equipment and medical supplies, to name a few. These raw materials may all include chrome due to the corrosion resistance of the element. Removal of chrome from current DoD products is unlikely but chrome should be eliminated as much as possible from future sources under DoD Pollution Prevention initiatives. However, in the meantime, the DoD must protect its workers and the public at a realistic risk level. This report examines the reality behind the toxicity and risk of chrome.

TABLE 3: SOURCES OF NAVAL OCCUPATIONAL EXPOSURE

Structure repair, paint removal, sanding
Construction, structure fabrication/repair
Metal cleaning mechanical/grinding/sanding etc.
Abrasive blast, glass bead/mineral grit/sand etc.
Barrel finishing
Acid cleaning
Degreasing
Chemical paint stripping
Open tank electroplating
Painting
Spray painting
Dip coating
Wipe coating
Spray coating
Metal machining, milling
Welding, resistance/oxyfuel/brazing/laser etc.
Hot work
Electric arc spraying
Flame spraying
Plasma cutting/arc cutting etc.
Plastics/rubber potting
Woodworking, cutting
Electronics repair
Graphic Arts, photo equipment
Packaging
Hazardous waste/sewer treatment
Equipment repair

EXPOSURE SCENARIOS

Brief Summary of Levels Encountered

Chromium is a natural element of the earth's crust and thus occurs in the air, water and soil at varying levels. The Agency for Toxic Substance and Disease Registry (ATSDR, 1993) reported the mean environmental concentrations as being 0.005 to 0.525 $\mu g/m^3$ in air, <1 to 30 $\mu g/l$ in surface water and 1 to 2000 mg/kg in soil. The Institute of Medicine quoted the estimated safe and adequate daily intake of chrome (Cr(III)) for adults at 50 to 200 μg/day, as a required micro-nutrient. Slooff *et al.* (1990) estimate the value at 2 to 8 μg/day in a review for the Netherlands. An enrichment factor of 3.5 to 8.1 due to anthropogenic activity as reflected in increased atmospheric loading was estimated in the ATSDR Profile (1993). The EPA Toxic chemical Release Inventory (TRI, 1994) listed chromium compounds as the 24th most released

chemical, in terms of total pounds released into the air, water, land and into underground injection wells, for the United States and its protectorates.

ATSDR (1993) referenced 1992 data indicating 9% of NPL sites had elevated chromium levels. Review of the 1996 HazDat database indicated chromium is a contaminant at 23% of 5158 Superfund and ATSDR public health assessment sites. In a separate unpublished analysis of 18 Air Force sites, four were found to be elevated and influencing the risk assessment. One was indicated to be a cancer risk and three were noncancer hazards. In each case chrome occurred with other heavy metal elements at the site (ORNL, 1995). Analysis of Air Force data in the Installation Restoration Program Information Management System (IRPIMS) (1995) indicated that chromium was the ninth most frequently detected compound.

Environmental Occurrence

Environmental chromium emissions occur from combustion of coal, manufacturing, metallurgy, metal treatment, wood preservation (frequently a serious EPA NPL site), incineration, mining, cooling tower discharges and pesticides. Within the DoD, metal treatment, painting/depainting, cooling towers and glass cleaning have been significant sources. Both soluble and insoluble forms of chromium have been used with compounds in multiple valence states. Exposure from environmental pathways are through drinking water contamination, direct soil contact and incidental dirt ingestion, inhalation of incinerator effluents (e.g., incineration of site soil, magnetic tape or copier toner disposal) and from uptake through plants and animals (ATSDR, 1993).

Speciation of the chromium valence state provides information on fate and transport and the health hazard implications. Chromium is impacted by the soil chemistry, redox potential, co-contaminants and presence of other naturally occurring materials. Chromium(III) has been described as virtually non-mobile above pH 5. Reduction of chromium(VI) to chromium(III) and precipitation as the oxide or hydroxide occurs. The ratio of chromium(III) to chromium(VI) is influenced by the redox potential and the pH. In one unpublished study at a Department of Energy (DOE) site, the ratio was found to be approximately 1.5% chromium(VI) as sampled from aerobic soils. In a study of two sites with varying pH areas at each site, the level of chromium(VI) varied from 0.5% at pH 4 to 15% at pH 7 (Davis *et al.*, 1994).

Chromium(VI) is considered to be soluble; however it can be reversibly absorbed onto soils under certain conditions. Soluble ionic forms of chromium(VI) formed in or added to soils and that present in natural waters will persist indefinitely unless chromate is removed by leaching, adsorption, precipitation, uptake by living cells or reduction to the trivalent form. Leaching has been known to occur (Bartlett, 1991). Oxidized manganese in soil was associated with oxidation of chromium(III) back to chromium(VI) (Bartlett and James, 1979). Both reduction and adsorption can occur simultaneously in many soils; therefore chromium(VI) disappearance can not be assumed to be attributed completely to either process. Chromate remaining in the oxidized form in soil can be considered immobilized, either because it has been precipitated or else bonded tightly by adsorption. Chromium(VI) can be protected from reduction by adsorption in some cases. In one study, however, highly weathered southern soils dominated by oxide-rich colloids adsorbed more chromium(VI) than less weathered northern acid soils; adsorption to these soils did not necessarily bind the chromium(VI) in such a way as to prevent its future reduction (Bartlett, 1991).

Microorganisms have been identified as routes for bioremediation through the reduction of chromium(VI). It has been postulated there could be biologically mediated oxidation of chromium(III) (Losi *et al.*, 1994). As an oxyanion, chromate, like nitrate, is a strong oxidizing agent in acid solutions, meaning that it is easily reduced. However, nitrate and chromate are much less effective oxidizing agents in neutral solutions or soils; both have a tendency to persist rather than be reduced. In the process of denitrification, various aerobic and anaerobic heterotrophic soil bacteria that metabolize available organic carbon have the ability to use nitrate as an electron acceptor and thereby reduce it. It seems likely that "dechromification" takes place by similar mechanisms (Bartlett, 1991).

Amacher and Baker (1982) showed that reduction of chromium(VI) by natural organic matter in soil was a first-order reaction with a half-life of several weeks. Chromate reduction by soil and water humic substances depletes available hydrogen and consequently is favored by acid additions. In natural soils, the reduction may be extremely slow, requiring years. Soil humic and fulvic acids in stable, moist fields do not readily reduce chromium(VI). Long-term isolation of chromium waste is a viable cleanup alternative if a permanent reducing environment and permanent immobilization of reduced chromium are present. As long as all chromium(VI) has been reduced and all chromium(III) is bound by decay-resistant organic polymers, the chromium will remain inert and immobile, provided that oxygen is excluded (Bartlett, 1991). Thus the fate and transport of chrome is highly dependent upon site specific conditions.

Chromium(VI) was found to be more toxic in aquatic plants in the assessment for ambient water quality standards than chromium(III). The toxicity was greater at high pH and low water softness. A bioaccumulation factor of 8500 was determined for algae, 125-200 for invertebrates and 3 for trout (EPA, 1985).

Exposure Pathways

Exposure assessments of chromium have shown unacceptable risks from ingestion of water, ingestion of soils, dermal contact to soils and inhalation transport of soils at waste sites. These situations have occurred for both residential and light industry scenarios. Ingestion uptake is mediated by the transport of chromium across membranes. Chromium(VI) is actively transported but chromium(III) has a much lower uptake (Owen, 1990). Trivalent chromium enters the cell only when extremely high concentrations exist outside the cell. In contrast, chromium(VI) exists as an oxy-anion (CrO_4^{-2}) that readily enters the cell by a nonspecific anion transport system (Coogan *et al.*, 1991). Once inside the cell, chromium(VI) is reduced ultimately to the trivalent form with intermediate oxidation states (e.g., Cr^{+5}) produced during reduction (De Flora and Wetterhahn, 1989). It is theorized that radicals formed during the reductive process as well as chromium(III) and other intermediates formed are ultimately responsible for the intracellular effects of chromium(VI) (Cohen *et al.*, 1990). Owen (1990) indicated a five-fold ratio of chromium(VI) over chromium(III) by oral absorption and a 2.5 fold ratio for inhalation absorption.

Human pathway bio-uptake of chromium is shown by different types of exposure monitoring. The circulating lymphocyte has been suggested as a good target cell type for monitoring exposure (Perera, 1987). Chromium tends to greater accumulate in the white blood cells (WBCs) than the red blood cells (RBCs) following either *in vitro* or *in vivo* exposure to chromate. The accumulation of chromium by WBCs supports their use as target cells in the development

of biomarkers for assessing exposure to chromates. Additionally, blood samples are easily obtainable from human populations (Coogan *et al.*, 1991). Urinary excretion of chromium (ore/elemental) following ingestion does not seem to be a good biomarker for chromium exposure assessment in humans. Studies have shown no correlation between increased ingestion and increased urinary excretion of chromium (Gargas *et al.*, 1994). Water soluble chromium(VI) from welding processes does seem to collect in both the urine and the blood (Bonde and Christensen, 1991). An upcoming method for testing human exposure to chromium seems to be the updated DNA-protein cross-links (DPX) test run on lymphocyte isolations from blood (Toniolo and Taioli, 1995).

At sites for which data is available, processes using chromium(VI) in the soluble form seems to have the potential for the most widespread impact. Soluble chromium(VI) would occur with corrosion prevention treatment in cooling towers or with chrome plating operations. Discharges in these situations could readily reach the groundwater or undergo uptake through plants and animals as chromium(VI).

From these studies, exposures to chrome at DoD sites is frequent but at relatively low levels. Because of the value conflict between micro-nutrient and potential hazardous material, it seems unlikely the criteria for environmental exposure to chrome will be further reduced to the point that contamination levels at DoD sites will result in significantly changed exposure assessments. Speciation of chrome valance states will need to be performed to assess exposure pathway bio-uptake levels. Additionally, chromium complexes at sites may need to be identified as metals in sulfide complexes have been implicated as being less bioavailable than other metal compounds in sediments (Bleiler, 1996).

LITERATURE SEARCH AND INFORMATION RETRIEVAL

Preliminary Chromium Information

Naval Medical Research Institute Toxicology Detachment (NMRI/TD), Wright-Patterson Air Force Base, OH provided initial information on the science review of chromium(VI) toxicology. This information included notes from public meetings concerning the proposed change, information on the impacts of the proposed change to the Navy and several journal articles concerning chromium(VI) fume effects in humans. Other preliminary information on chromium toxicity, physical characteristics and regulation was found in the ATSDR Toxicology Profile for Chromium (1993), EPA chromium publications (1984 and 1985) and the NIOSH Pocket Guide (1990). EPA's Integrated Risk Information System (IRIS) was searched for chromium criteria and background information.

Methods of Information Retrieval

The initial literature search was performed in the Medline and Toxline databases covering the last ten years. The rationale for this search focused on human chromate exposure, dose-response, known adverse effects, biomarkers and epidemiological studies. Chromium oxidation, uptake and distribution were also included. Additionally, queries were made using author/researchers identified as being in the process of current research designed to fill data

gaps (ATSDR, 1993). Articles identified in all searches were retrieved at local toxicological, technical or medical libraries.

The noncancer effects search was carried out in Medline and Toxline which was limited to articles published in 1991 or later. The focus of this search was to identify new effects data not published in the 1993 ATSDR Profile, which cites a few 1991 articles. Keywords used in this search focused on acute chromium exposures in animals and humans and systemic effects of chromium (e.g., immune, dermal). Additionally, data gap topics found in the Toxicological Profile (1993), such as chromium hypersensitivity and chromium effects on blood, were also addressed.

An iterative literature search was performed on years 1990 through 1996 in the Toxline database at the Wheaton Regional Library. The keywords used in this search included toxicological effects of chromium in general and also adverse effects of chromium(III).

A brief environmental levels search was performed in Medline and Toxline, covering the years 1966 through August 1996, due to the ready availability of these databases. The rationale focused on background levels, natural occurrence and environmental media (e.g., soil, sediment).

Additional Resources

Access to Docket H-054A, Chromium at OSHA Department of Labor in Washington D.C. provided valuable information on the driving force behind the proposed change as well as concerned parties' response to the proposal. Other valuable resources included Air Force databases (IRPIMS, 1995; ORNL, 1995) and government databases available on the World Wide Web (TRI, 1994; HazDat, 1996).

TOXICOLOGICAL HAZARD EVALUATION

Introduction

A toxicological assessment evaluates the hazards associated with the chemical in question and the amount of the chemical necessary to cause adverse effects. This section addresses biological responses to chromium, the chromium cancer risk to workers and the dose-response relationship of chromium in the body, including the no observed adverse effect level (NOAEL).

Noncancer Biological Response

Chromium as a toxicant has the ability to affect a number of body systems and functions. This evaluation of noncancer responses to chromium is arranged by system effects to allow for identification of target organs and determination of threat to humans exposed by various routes.

Respiratory Effects

The respiratory tract in humans is a major target of inhalation exposure to chromium compounds. Five individuals who had a history of contact dermatitis to chromium were exposed via a nebulizer to an aerosol containing 0.035 mg Cr(VI)/ml as potassium dichromate (ATSDR, 1993). A 20% decrease in the forced expiratory volume of the lungs was observed and was accompanied by erythema of the face, nasopharyngeal pruritus, nasal blocking, coughing and wheezing (Olaguibel and Basomba, 1989).

In a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes, workers experienced symptoms of sneezing, rhinorrhea, labored breathing, and a choking sensation when they were working over the chromate tanks. All five of the subjects had thick nasal and postnasal discharge and nasal septum ulceration or perforation after two to three months of exposure (Lieberman, 1941).

Intermediate or chronic duration occupational exposure to chromium(VI) may cause an increased risk of death due to noncancer respiratory disease. In a retrospective mortality study of 1,288 male and 1,401 female workers employed for at least six months in a chrome plating and metal engineering plant in the United Kingdom between 1946 and 1975, a statistically significant excess of deaths from diseases of the respiratory system (noncancer) was found for men and women combined. Exposure was mainly to chromium trioxide; however, precise exposure concentrations and data on smoking habits were not available. In another study of 1,212 male chromate workers who were employed for at least three months in three chromate plants in the U.S. during the years 1937-1940 and followed for 24 years, there was an increase of noncancer respiratory disease. The increased risk of death from respiratory effects correlated with duration of employment in chromate production, but no information on exposure levels, smoking habits, exposure to other chemicals or types of respiratory diseases were provided (Taylor, 1966). Chromate production workers in the United Kingdom had a statistically significant increase of death due to chronic obstructive airway disease; however, exposure concentrations were not known and reliable smoking data were not available (Davies *et al.*, 1991).

Occupational exposure to chromium(VI) as chromium trioxide in the electroplating industry caused upper respiratory problems. Nine men in a chrome plating facility reported seven cases of nasal septum ulceration. Signs and symptoms included rhinorrhea, nasal itching, soreness and epistaxis. The men were exposed from 0.5 to 12 months to chromium trioxide at concentrations ranging from 0.09 to 0.73 mg Cr(VI)/m^3 (Kleinfeld and Russo, 1965). Electroplaters in San Paulo, Brazil exposed to chromium trioxide vapors while working with hot chromium trioxide solutions had frequent incidences of coughing, expectoration, nasal irritation, sneezing, rhinorrhea and nosebleeds and developed nasal septum ulceration and perforation. Workers had been employed for less than one year; most of them were exposed to concentrations $\geq$ 0.1 mg Cr(VI)/m^3 (Gomes, 1972).

Numerous studies of workers chronically exposed to chromium(VI) compounds have reported nasal septum perforation and other respiratory effects. Workers at an electroplating facility exposed to 0.0001-0.0071 mg Cr(VI)/m^3 as chromium trioxide for an average of 26.9 months complained of excessive sneezing, rhinorrhea and epistaxis. Many of the workers had ulcerations and/or perforations of the nasal mucosa (Cohen *et al.*, 1974). Increases in chronic rhinitis, rhinitis with bronchitis, nasal ulcers and perforations were statistically significant in

workers from 54 chrome plating plants exposed to chromium(VI) compared to the control population (Royle, 1975). Workers had been exposed to chromium(VI) in fumes and dust. Air levels were generally less than 0.03 mg chromium(VI)/m^3 and dust levels were generally between 0.3 to 97 mg Cr(VI)/g. Nasal mucosal changes ranging from irritation to perforation of the septum were found among 77 employees of eight chromium electroplating facilities in Czechoslovakia where the mean level in the breathing zone above the plating baths was 0.414 mg Cr(VI)/m^3 (Hanslian *et al.*, 1967).

Occupational exposure to chromium(VI) and/or chromium(III) in other chromium-related industries has also been associated with respiratory effects. These industries include chromate and dichromate production, stainless steel welding and possibly ferrochromium production and chromite mining.

Nasal septum perforation, septal atrophy and ulcerations, sinusitis, pharyngitis and bronchitis were found among 65 men who worked in the production of dichromate and chromium trioxide for at least 1 year. Exposure concentrations were $\geq$0.01 mg Cr(VI)/m^3 in chromate production in Italy (Sassi, 1956). In a study of 97 workers from a chromate plant exposed to a mixture of insoluble chromite ore containing chromium(III) and soluble chromium(VI) as sodium chromate and dichromate, respiratory tract effects included perforations of the nasal septum (63%), chemical rhinitis (86.6%), chronic chemical pharyngitis (42.3%), laryngitis (10.35%), sinus, nasal or laryngeal polyps (12.1%). The number of complaints and clinical signs increased as the exposure to respirable chromium(VI) and chromium(III) compounds increased (Mancuso, 1951). In an industrial hygiene survey conducted in 1975, 60 ferrochromium workers exposed to chromium(III) and chromium(VI) (0.02-0.19 mg total Cr/m^3) over 15 years reported increased coughing, wheezing and dyspnea as compared to controls (Langard *et al.*, 1980).

In many of the studies attributing respiratory effects to chromium exposure, actual levels of chromium(VI) or chromium(III) to which the workers were exposed over time were unknown. Also, information on the contribution of cigarette smoking, exposure to other hazardous chemicals and previous employment histories to the observed effects were often not available.

In animals, chronic exposure to chromium(VI) compounds and mixtures of chromium(VI) with chromium(III) compounds have also resulted in adverse respiratory effects in animals. Rats exposed to either chromium(VI) alone as sodium dichromate or a mixture of chromium(VI) trioxide and chromium(III) oxide for 18 months showed interstitial fibrosis and thickening of the septa of the alveolar lumens. Chromium(VI) and chromium(III) together altered macrophage response; chromium(III) alone did not (Glaser *et al.*, 1986 and 1988). Significantly increased incidence of pulmonary lesions (lung abscesses, bronchopneumonia, giant cells and granulomata) was found in rats exposed chronically to a finely ground, mixed chromium roast material that resulted in airborne concentrations of 1.6-2.1 mg Cr(VI)/m^3 compared with controls. In the same study, guinea pigs exposed chronically to the chromium roast material along with mists of potassium dichromate or sodium chromate solutions resulting in 1.6-2.1 mg Cr(VI)/m^3 had significantly increased incidence of alveolar and interstitial inflammation, alveolar hyperplasia and interstitial fibrosis as compared to controls (Steffee and Baetjer, 1965). Therefore, gross and histopathological changes to the respiratory tract resulted from inhalation of chromium(VI) compounds or a combination of chromium(VI) and chromium(III) compounds.

Cardiovascular Effects

Information regarding cardiovascular effects in humans after inhalation exposure to chromium and its compounds is limited. In a chromate production facility in Italy where workers were exposed to concentrations $\geq$0.01 mg Cr(VI)/m^3, no cardiovascular abnormalities were found (Sassi, 1956).

Gastrointestinal Effects

Gastrointestinal effects have been associated with occupational exposure of humans to chromium compounds. In a U.S. electroplating facility, 5 of 11 workers reported symptoms of stomach pain; two had duodenal ulcers, one had gastritis, one had stomach cramps and one had frequent indigestion. Workers had been employed for an average of 7.5 years to a mean concentration of 0.004 mg Cr(VI)/m^3 (Lucas and Kramkowski, 1975). Workers were not compared to controls. In a study of 97 workers from a chromate plant where employees were exposed to a mixture of insoluble chromite ore containing chromium(III) and soluble chromium(VI) (as sodium chromate and dichromate), ten workers had ulcers and six had hypertrophic gastritis. Only two cases of gastrointestinal ulcers were found in 41 control individuals, who had the same racial, social and economic characteristics as the chromium exposed group (Mancuso, 1951). In an Italian chromate production facility where exposure concentrations were $\geq$ 0.01 mg Cr(VI)/m^3, 15.4% of the 65 workers who were employed in the production of dichromate and chromium trioxide for at least one year had duodenal ulcers and 9.2% had colitis. The ulcers were considered to be due to exposure to chromium. Gastric mucosa irritation leading to duodenal ulcer was found in 21 of 90 workers engaged in the production of chromium salts (Sassi, 1956). Most of these studies reporting gastrointestinal effects did not compare the workers with appropriate controls.

Hematological Effects

Hematological evaluations of workers occupationally exposed chromium compounds and rats exposed to chromium have yielded equivocal results (ATSDR, 1993).

Hepatic Effects

Chromium(VI) has been reported to cause severe liver effects in four of five workers exposed to chromium trioxide in the chrome plating industry. Derangement of the liver cells, necrosis, lymphocytic and histiocytic infiltration and increases in Kupffer cells were reported (Pascale *et al.*, 1952). Hepatic effects in animals after inhalation exposure to chromium or its compounds were minimal and not considered to be adverse.

Renal Effects

Studies of the renal function in chrome platers, whose exposure is mainly to chromium(VI) compounds, have yielded equivocal results while occupational exposure to chromium(III) does not appear to be associated with renal effects (ATSDR, 1993).

Immune Endpoints:

Acute reactions have been observed in chromium sensitive individuals exposed via inhalation. A 29-year-old welder exposed to vapors from chromium trioxide baths and to chromium and nickel fumes from steel welding for ten years complained of frequent skin eruptions, dyspnea and chest tightness. Exposure to 0.029 mg Cr(VI)/ml as sodium chromate caused an anaphylactic reaction characterized by dermatitis, facial angioedema, bronchospasms accompanied by a tripling of plasma histamine levels and urticaria (Moller *et al.*, 1986).

Anaphylactic reactions were observed in five individuals, who had a history of contact dermatitis to chromium, after exposure via nebulizer to an aerosol containing 0.035 mg Cr(VI)/ml as potassium dichromate. Exposure resulted in decreased forced expiratory volume, facial erythema, nasopharyngeal pruritus, nasal blocking, cough and wheezing (Olaguibel and Basomba, 1989). Challenge tests with fumes from various stainless steel welding processes indicated that the asthma observed in two stainless steel welders was probably caused by chromium or nickel, rather than by irritant gases produced by the welding process (Keskinen *et al.*, 1980). Chromium-induced asthma may occur in some sensitized individuals exposed to elevated concentrations of chromium in air, but the number of sensitized individuals is low and the number of potentially confounding variables in the chromium industry is high (ATSDR, 1993).

Park *et al.* (1994) reported four cases of occupational asthma caused by chromium salts on a bronchial provocation test. All patients were ex-smokers employed in metal plating, cement and construction industries. All reported asthmatic symptoms with or without rhinitic symptoms during and after working hours; there were no reports of contact dermatitis. Adverse symptoms were alleviated in three of four patients following administration of antiasthmatic medications and removal from chrome exposure. Researchers concluded chromium salt was the specific etiological agent causing occupational asthma in these cases. However, exposure levels were not reported, the study size was very small and, as the patients were all ex-smokers, the study was confounded.

Snyder *et al.* (1996) reported decreased ability of individuals in Hudson County, NJ, to produce IL-6. IL-6 is produced by mononuclear cells isolated from blood and cultured with pokeweed mitogen. Blood samples were taken from 46 Hudson County residents and 47 controls. IL-6 levels from the Hudson County mononuclear cells were only 64% of the control levels; this decrease was found to be highly significant ($p<0.001$). Hudson County had been a major processing site for chromium ore; processing consisted of converting chromium(III) ore to soluble chromium(VI) compounds. Waste residues were used for landfill and incorporated into building materials throughout the county. All Hudson County subjects either lived or worked in Jersey City , an urban environment. All subjects who served as controls lived and worked in suburban or rural areas. Therefore, it is possible that the differences detected in IL-6 levels resulted from exposures to an urban versus a rural or suburban environment and did not result from chromate exposure specifically.

Immune effects for chromium(VI) have been observed in rats. Rats exposed to 0.05 mg Cr(VI)/m^3 as sodium dichromate for 90 days had increased percentages of lymphocytes and granulocytes as well as increased macrophage number, size and activity. At 0.2 mg Cr(VI)/m^3, mitogen-stimulated T-cell response increased. Low levels (0.2 mg Cr(VI)/m^3) of sodium dichromate stimulated the rat humoral immune system (Glaser *et al.*, 1985).

Dermal Endpoints

One biological endpoint of importance is skin hypersensitivity or dermatitis. These lesions have been reported to persist for several years in many subjects and significant work time loss has occurred. The chronicity of chromium dermatitis together with the unavailability of specific treatment is the basis of the relatively poor prognosis generally given. Maintenance of chromium levels as low as possible in the environment is emphasized (Bagdon and Hazen, 1991).

Chromium contact dermatitis is a delayed hypersensitivity reaction classified as a type IV cell-mediated immune response. The interaction involves binding of haptens with T-lymphocytes with transformation into memory and effector cells. Upon a secondary chromium challenge of the effector cells, a cascade of mediators cause inflammation of the skin (Bagdon and Hazen, 1991).

The potent skin allergenicity of chromium has been well documented in the literature and chromium compounds have been reported to be the most frequent sensitizing agent in man (Haines and Niebor, 1988; Burrows, 1983; Polak, 1989). Only minute quantities of chromium are required to penetrate the skin and elicit a positive hypersensitivity reaction in susceptible individuals. Using a patch dose of 20 μg of sodium chromate, only 2 μg was required to evoke a positive skin reaction in hypersensitive subjects (Pedersen *et al.*, 1970).

Hexavalent chromium has been shown to be a potent skin sensitizer in guinea pig sensitization tests (Maurer *et al.*, 1979; Magnusson and Kligman, 1969). Allergic contact dermatitis from chromium is a distinct clinical entity that arises from numerous types of occupational exposure and has been extensively reviewed (Haines and Niebor, 1988; Burrows, 1983; Adams, 1983; Burrows, 1972; Zelger, 1964). It is important to recognize there is no relationship between the classic chromium ulcer lesion that occurs in skin and mucous membranes and allergic sensitization of skin.

One approach to assessing the susceptibility of populations to chromium-induced dermatitis is use of the patch test titration technique in which successively decreasing concentrations of chromium are used to determine the threshold concentration. In several studies involving challenge tests in human subjects, the threshold concentration for skin hypersensitivity to hexavalent chromium in 8% of individuals was determined to be 10 ppm (Bagdon and Hazen, 1991). Skin hypersensitivity data for trivalent compounds in humans is limited and the sensitization potency varies with the trivalent chromium salt tested. Using sulfate and nitrate salts, an approximate threshold concentration for evoking skin hypersensitivity in 10% or less of the population by trivalent chromium compounds is 500 ppm. This threshold level is 50-fold higher than that determined for hexavalent chromium compounds.

Based on epidemiological surveys using the positive patch test rate to hexavalent chromium as an index, allergic contact dermatitis is a common acute effect resulting from exposure of the skin to low levels of chromium. From a review of these surveys, it has been determined for concentrations of hexavalent chromium in solution of less than 0.001% (10 mg/l), the incidence of contact dermatitis will be reduced to less than 10% in chromium sensitive subjects (Bagdon and Hazen, 1991).

Other factors that add to the complexity of evaluating chromium induced skin hypersensitivity are the variable patterns of the skin lesions, persistence and lack of reversibility or periodic exacerbations. Lack of a strict dose-response relationship, long latency for manifestation of skin lesions in some individuals after exposure and lack of specific treatment other than removal from the contaminated environment also complicate the evaluation. Other effects on skin, such as severe pruritis, also occur (Bagdon and Hazen, 1991).

Chromate sensitization was elicited from cement containing iron sulfate (Bruze *et al.*, 1990). Allergic contact dermatitis from chromate was reported in three workers exposed to cement containing chromium at levels between 2-40 μg/g cement (about 0.2%) and iron sulfate. From studies of cement workers, 8 to 9% are allergic to chromium on patch testing but have no history of dermatitis. Chromium sensitivity in cement workers seems to develop after many weeks or even years of irritation, which allows the chromium to get into the skin and produce the allergic reaction (Gochfeld, 1991a).

Overall, the incidence of chrome dermatitis is low. From years of experience in patch testing many patients with chromium, about 1 to 2% test positive, which compare pretty favorably with other contact allergens. For workers, the incidence of chrome dermatitis is low, probably about 1% or less (Gochfeld, 1991a).

Neurological Endpoints

In a chrome plating plant where poor exhaust resulted in excessively high concentrations of chromium trioxide fumes, workers experienced symptoms of dizziness, headache and weakness when they were working over the chromate tanks (Lieberman, 1941). Such poor working conditions probably no longer exist due to improvements in industrial hygiene over the years. No information was located regarding neurological effects in humans or animals after inhalation exposure to chromium(III) compounds or in animals after inhalation exposure to chromium(VI) compounds.

Developmental Endpoints

No studies were located regarding developmental effects in humans after inhalation exposure to chromium (ATSDR, 1993).

Reproductive Endpoints

Sixty-one electrowelders had oligospermia. Sperm concentrations were less than 40 million/ml among 54% of welders and were less than 20 million/ml among 25% of welders (Haneke, 1973 as cited in Bonde, 1993). Rachootin and Olsen (1983) reported difficulties in conception and Mortensen (1988) cited reduced semen quality in metal welders. Bonde (1993) concluded that welding, in general, represents a hazard to the fecundity of male welders.

Experimental studies document spermatotoxic effects of hexavalent chromium in rats which include testicular atrophy, reduced epididymal sperm count (Ernst, 1990) and reduced epididymal sperm motility (Ernst and Bonde, 1992). Testicular cell degeneration was reported

in rabbits (Behari *et al.*, 1978). The lowest observed effect level (LOEL) in rats is 0.5 mg Cr(VI)/kg following intraperitoneal administration five days a week for eight consecutive weeks.

Genotoxic Endpoints

Studies involving electroplaters and welders report a higher incidence of chromosomal aberrations in lymphocytes of workers than in controls. In one study, a causal relationship between chromium exposure and the observed effects could not be established because the exposure was confounded by co-exposure to nickel and manganese (Elias *et al.*, 1989). The frequency of sister chromatid exchanges in the lymphocytes of 12 workers exposed to chromium(VI) as chromic acid fumes from plating were significantly increased, especially among young workers (≤22 years of age) as compared to controls (Stella *et al.*, 1982). Significantly increased incidence of chromosomal aberrations in peripheral lymphocytes were found in workers exposed to chromium(VI) as chromium trioxide in two of four electroplating plants. Electroplaters exposed to 0.008 mg Cr(VI)/m^3 had increases in chromosomal aberrations and sister chromatid exchanges. However, high levels of nickel as well as chromium were found in hair and stool samples when compared to controls (Deng *et al.*, 1988).

Hence, chromium and its compounds, particularly chromium(VI), may cause chromosomal effects in exposed workers. This indicates carcinogenic potential because interactions with DNA have been linked with the mechanism of carcinogenicity.

In rats that inhaled chromium fumes from powdered chromium metal at 1.84 or 0.55 mg Cr(0)/m^3, five hours/day, five days/week, for one week or two months, respectively, had increased frequencies of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes (Koshi *et al.*, 1987). Other genotoxic studies are cited in another section, Cancer Mechanisms Observed.

No Observed Adverse Effect Levels

The NOAEL is reported for humans in terms of the reference dose (RfD). In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. The RfD is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis but may not exist for other toxic effects such as carcinogenicity.

The EPA (1984 and 1985; IRIS, 1995) reported an oral RfD for chromium(VI) soluble salts of 0.005 mg/kg-day. This is based on a one year drinking water study where rats were dosed with 25 mg/l chromium as K_2CrO_4 (MacKenzie *et al.*, 1958). The NOAEL was determined to be 25 mg/l of chromium as no significant adverse effects were seen in appearance, weight gain or food consumption. Also, there were no pathologic changes in the blood or other tissues in any treatment group. The uncertainty factor of 500 takes into account a factor of ten for extrapolation from animals to humans, a factor of ten for interhuman variability and an additional factor of five to compensate for less-than-lifetime exposure duration.

Confidence in the MacKenzie *et al.* (1958) study is low because of the small numbers of animals tested, the small number of parameters measured and the lack of toxic effect at the highest dose treated. Confidence in the database and RfD is low because the supporting studies are of equally low quality and teratogenic and reproductive endpoints are not well studied. The oral RfD for chromium(VI), may change in the near future pending the outcome of a further review now being conducted by the EPA RfD/RfC work group.

For chromium(III), an oral RfD of 1.0 mg/kg-day has been established by EPA using a study in which rats were fed 5% Cr in the diet five days/week for 600 feedings (1800 mg/kg body weight average total dose). No toxic effects were seen at any dose (LaVelle, 1991). An uncertainty factor of 100 was applied; a factor of 10 was assigned for animal to human variation and another factor of 10 was for inter-human variation to take into account sensitive populations. A modifying factor of 10 was applied for three reasons which caused uncertainty in the NOAEL. First, the possibly adverse endpoints seen in the 90 day study were not looked for after the two year study. Second, as the absorption of chromium(III) is low, there was "considerable potential" for variation in absorbed dose. Third, the histological exam was considerably delayed after exposure as all animals were allowed to die naturally (IRIS, 1994).

A NOAEL of 0.001 mg Cr(VI)/m^3 for the respiratory route of exposure to Cr(VI) was cited for humans (ATSDR, 1993). In this study, respiratory adverse effects including a smeary and crusty septal mucosa and atrophied mucosa were reported at 0.002 mg Cr(VI)/m^3 in 43 chrome plating workers exposed to chromium trioxide for 0.2 to 23.6 years. At 0.02 to 0.046 mg Cr(VI)/m^3, nasal mucosal ulceration and septal perforation occurred in individuals (Lindberg and Hedenstierna, 1983).

Cancer Risks

Cancer Mechanisms Observed

Oxyanions, such as chromium(VI), are actively transported into cells by the sulfate transport system, resulting in high intracellular concentrations (Costa, 1991; Sugiyama, 1991; De Flora and Wetterhahn, 1989; Costa *et al.*, 1984; Jennette, 1979). The hexavalent chromium reacts with a number of reducing agents in cells including glutathione, hydrogen peroxide, ascorbate and microsomal enzymes and ribonucleotides (Sugiyama, 1991; Goodgame and Joy, 1987). Chromium(VI) is eventually reduced to the kinetically inert and stable trivalent form (Arslan *et al.*, 1987; Connett and Wetterhahn, 1983). During its reduction, intermediate oxidation states of chromium are formed; the reduction process itself, as well as the formation of these intermediate states of chromium, are thought to be important in chromium genotoxicity.

It is believed that the tetrahedryl geometry of chromium(VI) allows easy transport across membranes by anion carriers. A small proportion of chromium(III) is taken into cells and may eventually react with the DNA, forming different adducts than those formed when chromium(VI) is reduced *in situ* (Witmer, 1991).

The hexavalent form of chromium has been shown to produce a variety of lesions in the DNA of mammalian cells, including single-strand breaks and other chromosomal lesions (Wise *et al.*, 1992), alkali-labile sites, DNA-DNA and DNA-protein cross-links (Tsapakos *et al.*, 1983;

Sugiyama *et al.*, 1986a and 1986b). Chromium is a very broad-acting genotoxic agent, evident by its ability to directly induce lesions as well as to indirectly generate oxygen radicals and reactive intermediates (Connett and Wetterhahn, 1983). In fact, chromate has proved positive in almost every genotoxicity assay in which it has been tested.

DNA-protein complexes produced by chromium compounds have not been well studied in the past. These lesions, unlike strand breaks and other DNA lesions that are readily repaired, are relatively persistent in the cell (Sugiyama *et al.*, 1986a and 1986b). Due to their lack of repair, DNA-protein complexes are likely to be present during DNA replication and may constitute a block to the replication machinery. Deletions which may result could be important in chromium carcinogenesis if the deleted DNA sequences code for a tumor-suppresser gene or are involved in the regulation of these important genes (see Figure 1).

Chromium(III) may possibly contribute to mutagenesis (Snow, 1991; Warren *et al.*, 1981; Elias *et al.*, 1986), genotoxicity (Nakamuro *et al.*, 1978) and chromium-mediated carcinogenesis. However, because of chromium's complex intracellular metabolism, molecular mechanisms of chromium-induced genotoxicity are not well understood (Snow, 1991). This information is based on reports that chromium(III) alters the interaction between the DNA template and the polymerase such that the binding strength of the DNA polymerase is increased -and the fidelity of DNA replication is decreased (Sugiyama *et al.*, 1986a and 1986b; Costa, 1991; Cohen *et al.*, 1993).

There is some uncertainty in the scientific literature as to what binding of chromium to DNA does to the cell to increase the incidence of cancer. Currently, little is known about the biological consequences of DNA-protein cross-link formation in the cell other than it is produced by several carcinogenic agents of environmental and occupational significance (Oleinick *et al.*, 1987). The DNA-protein cross-link is bulky and may result in large deletions during DNA replication, possibly leading to the inactivation or loss of DNA sequences of such importance as those involved in tumor suppression. Very few studies have attempted to examine this lesion in any detail (Miller *et al.*, 1991). A thorough study of DNA-protein cross-links may lead to a more basic understanding of chromatin structure and the three-dimensional orientation of nuclear proteins.

Studies have demonstrated that a DNA polymerase complex could not replicate over a DNA-protein complex that blocked its procession; these studies provide insight into the potentially deleterious effects of DNA-protein cross-links (Bedinger *et al.*, 1983; Miller and Costa, 1990).

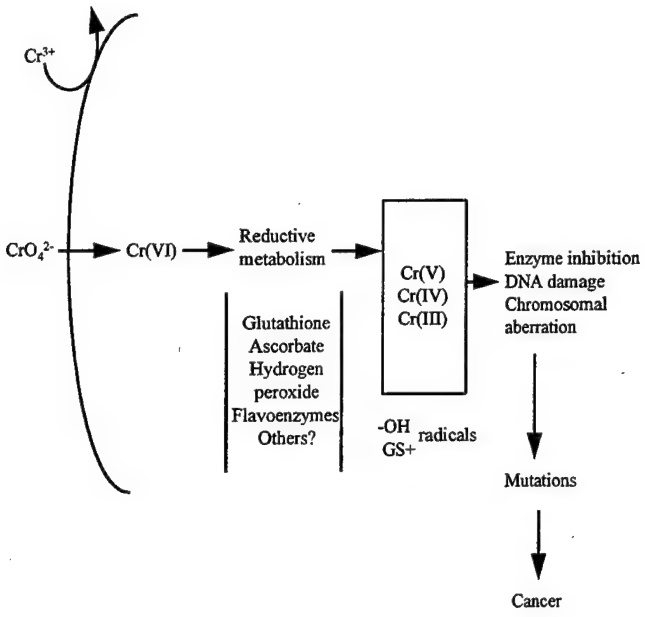

FIGURE 1: CELLULAR REDUCTION OF CHROMIUM(VI)
Adapted from Sugiyama, 1991.

Cancer Slope Factor

A cancer slope factor is as a plausible upper-bound estimate of the probability of an individual developing cancer as a result of exposure to a particular level of a potential carcinogen. Slope factors should always be accompanied by the EPA's weight of evidence classification to indicate the strength of the evidence that the agent is a human carcinogen.

EPA classifies chromium(VI) as a Class A Human Carcinogen on the basis of several occupational epidemiological studies, consistent across investigators and countries, which established a dose-response relationship between chromium exposure and lung cancer. Chromium workers are exposed to both chromium(III) and chromium(VI); however, because only chromium(VI) has been found to be carcinogenic in animal studies, EPA concludes that only chromium(VI) should be classified as a human carcinogen. Using the 1975 Mancuso data and multistage dose extrapolation, EPA established a lifetime inhalation unit risk of 0.012 $(\mu g/m^3)^{-1}$ or a cancer slope factor of 42 $(mg/kg\text{-}day)^{-1}$ for chromium(VI) (IRIS, 1995).

Applicability To Human Exposure/Epidemiology Information

Occupational exposure to chromium(VI) compounds in a number of industries has been associated with increased risk of respiratory system cancers, primarily bronchogenic and nasal. Among the industries investigated in retrospective mortality studies are chromate production, chromate pigment production and use, chrome plating, stainless steel welding, ferrochromium alloy production and leather tanning. Studies in chromate production workers, who are exposed to a variety of both hexavalent and trivalent chromium compounds, and chromate pigment industries, where exposure is mainly to chromium(VI), have consistently demonstrated

an association with respiratory system cancer. Studies in chrome platers, who are exposed to chromium(VI) and other agents including nickel, generally support the conclusion that chromium(VI) is carcinogenic. Studies in stainless steel welders exposed to chromium(VI) and other chemicals, and ferrochromium alloy workers, who are exposed mainly to chromium(0) and chromium(III) as well as some chromium(VI), were inconclusive (ATSDR, 1993).

There are numerous studies demonstrating an increased risk of lung cancer due to chromium(VI) in chromate production industry despite limitations in some studies. Studies of workers engaged in the production of chromate pigments also have consistently shown an association with increased risk of lung cancer. A Navy/Industry Task Group report (1995) stated electroplating and welding are two occupational groups that potentially have chromium(VI) exposure. Therefore, epidemiology studies in these exposure groups have been reviewed.

Chrome Plating

Studies on the risk of cancer in chrome platers have produced both positive and negative results but they generally support the conclusion that chromium(VI) is carcinogenic. In an analysis of the cause of death among 172 white male and 49 white female employees engaged for at least ten years in die-casting and electroplating in a U.S. automobile hardware manufacturing plant, statistically significant increases were found for all cancers in men, for respiratory system cancers in men and women and for lung cancer in men and women (Silverstein *et al.*, 1981). A specific causative agent could not be identified from this study and exposure concentrations were not analyzed. Although the smoking habits of the workers were not assessed, the lack of an increase in other smoking-related illnesses (emphysema, coronary heart disease, bladder cancer) was considered evidence that the increased risk of lung cancer was not due to smoking.

A study of 276 male electroplaters who were exposed to chromic acid and had worked for at least 3 months within 10 years prior to 1959 at two U.S. military aircraft maintenance bases was conducted. The electroplaters were followed through 1977. No excess cancer compared to national rates were found (Dalager *et al.*, 1980).

A mortality study of 2,689 chrome platers employed for at least six months in a plant in the United Kingdom between 1946 and 1975 found excess risks for several types of cancer, compared with the mortality rates for England and Wales. Statistically significant excesses were found among male workers for stomach cancer, primary liver cancer, nose and nasal cavity cancer, cancer of the lungs and bronchi and all cancers. Most of the excesses were attributed to working the chrome baths where exposures were mainly to chromium(VI) as chromic acid. Exact exposure concentrations were not known. Smoking habit data were not available (Sorahan *et al.*, 1987).

Results of a retrospective cohort study of 178 workers in nine Italian chrome plating plants suggest an association between lung cancer and "hard" (thick) chrome plating as opposed to "bright" (thin) chrome plating. The cohort members had been employed for at least one year during 1951 to 1981. Death from any cancer was observed in 7 of the 116 hard platers compared with 2.7 expected; this was significant. Workroom monitoring in 1980 for hard platers, when improvements in industrial hygiene had already been made, revealed an average

concentration of 0.0007 mg Cr(VI)/m^3 as chromic acid near the baths and 0.003 mg Cr(VI)/m^3 in the middle of the room. Prior to improvements in industrial hygiene, airborne levels of total chromium near the baths have been reported to be 0.06 mg/m^3 for hard plating (Guillemin and Berode, 1978).

Exposure to chromium(VI) in the electroplating industry is associated with lung, nasal and possibly stomach cancer; it may also be associated with oral cavity cancer. In 77 employees of chromium electroplating factories in Czechoslovakia, 16 oral cavity growths were found in 14 individuals. The growths were papillomas which were considered to be precancerous lesions. All papillomas were found to contain chromium. The average breathing zone concentration of chromium(VI) above the plating baths was 0.414 mg Cr(VI)/m^3 (Hanslian *et al.*, 1967).

Stainless Steel Welding

Inconclusive results have been obtained in studies of stainless steel welders. A study of 1,221 stainless steel welders in the former West Germany found no increased risks of lung cancer or any other specific type of malignancy compared with 1,694 workers involved with mechanical processing (not exposed to airborne welding fumes) or with the general population (Becker *et al.*, 1985). A study of 234 workers from eight Swedish companies who had welded stainless steel for at least five years during the period of 1950-1965 and were followed until 1984 found five deaths from pulmonary tumors compared with two expected based on the national rate. The excess was not statistically significant. However, when the incidence of lung cancer among the stainless steel welders was compared to a control group from within the company, a significant increase was found after adjusting for age. The average chromium(VI) concentration in the workroom from stainless steel welding, determined in 1975, was 0.11 mg/m^3 (Sjogren *et al.*, 1987). Smoking was not a confounding factor in the comparison with the internal control group.

Overall, human and animal studies support an increased risk of lung cancer due to chromium(VI). In lab animals, chronic inhalation studies provide evidence that chromium(VI) is carcinogenic in animals. Mice were exposed to 4.3 mg Cr(VI)/m^3 as calcium chromate. There was a 2.8-fold greater incidence of lung tumors compared to controls (Nettesheim *et al.*, 1971). Lung tumors were observed in 3 of 19 rats exposed to 0.1 mg Cr(VI)/m^3 as sodium dichromate for 18 months. Tumors included two adenomas and one adenocarcinoma. No lung tumors were observed in controls or the rats exposed to 0.05 mg Cr(VI)/m^3 or less (Glaser *et al.*, 1986 and 1988). Results were statistically significant.

Recent Research Efforts

Noncarcinogenic and carcinogenic effects have been reported for chromium(VI) and chromium(III) for both humans and animals (ATSDR, 1993). An update of the literature using Medline and Toxline for the years 1991 through 8/1996 was performed. The results for recent research efforts are reported in this section to update the 1993 ATSDR Toxicological Profile for Chromium. From the literature that was collected during this effort, the only apparent addition to these two figures concerns genotoxic/DNA mutation effects for chromium(III).

Chromium(III) can react slowly with both nucleic acids and proteins and can be genotoxic. The genotoxicity of chromium(III) *in vitro* was studied using DNA replication assays and *in vivo* by calcium chloride-mediated transfection of chromium-treated DNA into *E. coli*. When DNA replication was measured on a chromium(III)-treated template using purified DNA polymerase (either bacterial or mammalian), both the rate of DNA replication and the amount of incorporation per polymerase binding event were greatly increased relative to controls. When transfected into *E. coli* Cr(III)-treated M13mp2 bacteriophage, DNA showed a dose-dependent increase in mutation frequency. These results suggest that chromium(III) alters the interaction between the DNA template and the polymerase such that the binding strength of the DNA polymerase is increased and the fidelity of DNA replication is decreased. These interactions may contribute to the mutagenicity of chromium ions *in vivo* and suggest that chromium(III) can contribute to chromium-mediated carcinogenesis (Snow, 1991).

Other researchers also postulated that chromium(III) is involved in DNA-protein cross-links (Voitkun *et al.*, 1994) and that chromium(III) reacts with DNA (Salnikow *et al.*, 1992). Since a substantial portion of the chromium bound to DNA was released by treatment with EDTA, this suggests that chromium (III) is the major oxidation state of Cr bound to DNA. Chromium(III) stimulated the formation of amino acid-DNA and protein-DNA complexes *in vitro*. Similar results were found in intact cells. Researchers suggested that chromium(III) is involved directly in the formation of DNA-protein complexes in intact cells.

Several other review articles report genotoxicity for chromium(III) and that chromium(III) is capable of causing DNA damage under certain conditions and may be mutagenic (Stearns *et al.*, 1995). Chromium(III) forms Cr-nucleotide complexes with dissolved nucleic acids (Magos, 199l). Chromium(III) can lead to genotoxic damage in phagocytes (Anderson, 1983; Cohen *et al.*, 1993). Chromium(III) has been shown to produce genotoxic responses (Cohen *et al.*, 1993). Although the trivalent chromium compounds are not as active as the hexavalent compounds in cellular systems due to poor uptake, chromium(III) reacts *in vitro* with DNA. Trivalent Cr has been shown to bind to isolated nuclei *in vitro* (Koster and Beyersmann, 1985), to interact with nucleotides and nucleic acids (Denniston and Uyeki, 1987; Wolf *et al.*, 1989), to produce DNA-protein cross links (Snow, 1991) and to modify the fidelity and kinetics of DNA replication (Snow and Xu, 1989 and 1991). In summary, select studies suggest that chromium(III) can bind to DNA and modify replication, possible mechanizing carcinogenesis.

Assessment of Chromium(III) Risk

The scientific literature does not support a unit risk value for chromium(III) (Mancuso, 1951 and 1975; Mancuso and Hueper, 1951; Hayes, 1979a; Hayes *et al.*, 1979; IRIS, 1994; Gibb, personal communication, 1996). However select studies and/or review articles support that chromium(III) is carcinogenic in humans (ATSDR, 1993; Kusiak *et al.*, 1993; Pokrovskaya and Shabynina, 1973) and animals (ATSDR, 1993). The ATSDR profile reports incidence of cancer in humans by inhalation and in animals by oral administration.

Several researchers reported an increased incidence of cancer in workers exposed primarily to chromium(III) or to chromium(III) alone. Kusiak *et al.* (1993) reported a statistically significant excess of the stomach in Ontario gold miners compared to controls. The workers were exposed to trivalent chromium in the form of chromium mica (fuchsite) and chrome oxide (chromite) in addition to other chemicals. Researchers eliminated the effect of smoking in

production of cancer because they indicated that "smoking and alcohol consumption are not likely explanations for the increased mortality from stomach cancer in Ontario gold miners" because they observed no difference in smoking habits between the experimental and control groups. They also determined that their results were not due to any other chemical in their evaluation and gave reasons for this. They concluded that "chromium may then be a causative agent, or closely associated with it."

In the ferrochromium industry, where exposure is primarily to chromium(III) and lesser amounts of chromium(VI) (ATSDR, 1993), increased incidence of cancers have been reported in workers. Mortality rates from all malignant tumors, including esophagus, gastrointestinal and uterine tumors, among people who had worked in chromium ferroalloy production were higher with respect to the population of the city in almost all age groups (Pokrovskaya and Shabynina, 1973).

These two previously cited studies suggest chromium(III) may be, in fact, involved in causing cancer. Additional support for this conclusion was provided by the early work of Mancuso and Hueper (1951) who proposed that exposure to trivalent forms, such as chromite ore (Cr(III)), may be associated with excess risk for lung cancer among workers in the chromium chemical production industry. Mancuso and Hueper arrived at this conclusion based on detailed job histories; they assigned a weighted average exposure to soluble (Cr(VI)) and insoluble chromium (Cr(III)) compounds for the study group. As only a small proportion of all workers were predominantly exposed to soluble chromium and none of the lung cancer deaths had been predominantly exposed to soluble chromium, they concluded that the data "suggest that the inhalation of dust of chromite ore (i.e., insoluble chromium) might not be without importance in the causation of lung cancers (Mancuso and Hueper, 1951 as reported in Hayes, 1979a).

Grogan (1957) pointed out that body stores of trivalent chromium may operate as a depot of chromium which is gradually transformed into the hexavalent form through the oxidative action of biologic processes. The experimental studies, however, give little support to the hypothesis (Hayes, 1979a).

Even though select studies support that chromium(III) is carcinogenic, no unit risk factor for chromium(III) has been published for it by EPA (IRIS, 1994). EPA derived the unit risk value for chromium(VI) of 1.2×10^{-2} $(\mu g/m^3)^{-1}$ for inhalation based on the 1975 Mancuso study. Mancuso indicated the lung cancer death rates were based on total chromium (both soluble (Cr(VI)) and insoluble (Cr(III)) chromium). He indicated "the data are consistent with the lung cancer risk being a function of both the soluble and insoluble chromium, i.e., the total chromium, rather than to one class of chromium compound". However, when EPA did the derivation of the unit cancer risk value, "the cancer mortality in Mancuso (1975) was assumed to be due to chromium(VI), which was further assumed to be no less than one-seventh of total chromium (IRIS, 1995)".

Gibb (personal communication, 1996) indicated he did not work on deriving a chromium(III) unit risk value yet, even though they have chromium(III) data in the Johns Hopkins University study. As previously mentioned, he did derive a unit risk value for chromium(VI), based on the incidence of cancer in the Johns Hopkins University study.

The Hayes *et al.* (1979) study did not include chromium exposure data; no unit risk value was derived from Hayes' data by EPA. The Mancuso (1975) data was used to derive the unit risk value for chromium (IRIS, 1995).

RISK CHARACTERIZATION

Comparison of Recent Information to Existing Criteria

The EPA estimated a lung unit cancer risk for hexavalent chromium of 1.2×10^{-2} $(\mu g/m^3)^{-1}$ based on the Mancuso (1975) mortality study (IRIS, 1995). OSHA concluded that the best data currently available for quantitative risk assessment of hexavalent chromium come from the Mancuso cohort and the Hayes *et al.* cohort (1979) (Braver *et al.*, 1985). Both these studies had unique strengths and weaknesses; OSHA concluded that these studies have equal value for developing quantitative risk estimates and that either would be sufficient alone as the basis for estimating risk (ICF Kaiser, 1995).

Using a significant cancer risk of 1/1000 (used by the courts for benzene) and the EPA-derived unit risk value developed from the Mancuso study of 1.2×10^{-2} per $\mu g/m^3$, an exposure value of 0.08 $\mu g/m^3$ for continuous lifetime exposure to chromium was produced (Public Citizen's Health Research Group and the Oil, Chemical and Atomic Workers International Union, 1993; Industrial Union Department, 1980).

Johns Hopkins University (JHU) School of Public Hygiene and EPA conducted a joint study concerning the mortality of chromate production workers at a plant in Baltimore, MD. Using the JHU data, Gibb (1996b) derived a nonsmoking unit risk of 3.63×10^{-3} $(\mu g/m^3)^{-1}$. Utilizing a 1/1000 significant cancer risk value and this new unit risk value derived by Gibb, the chromium(VI) exposure concentration was 0.275 $\mu g/m^3$.

OSHA determined that the most reliable estimates of lung cancer risk from occupational exposure to hexavalent chromium range between those calculated from the Hayes cohort and those determined from the Mancuso cohort with the data from the high exposure group omitted. Table 4 contains estimates of lifetime risk of cancer from 45 years of occupational exposure to hexavalent chromium at various air concentrations based on OSHA's analyses of the Mancuso and Hayes cohorts. As indicated in this table, OSHA's estimate of additional risk of lung cancer from 45 years of occupational exposure to 1 $\mu g/m^3$ ranges from 1.8 to 8.9 per thousand. Their estimate of the additional lung cancer risk from occupational exposure to 0.5 $\mu g/m^3$ ranges from 0.9 to 4.4 per thousand (ICF Kaiser, 1995).

The JHU data as quantified by Gibb, the Mancuso study as quantitated by the EPA and the Mancuso and Hayes studies as quantitated by OSHA strongly support reducing the current OSHA PEL of 100 $\mu g/m^3$ for chromium(VI) exposure to 0.5 $\mu g/m^3$. This would reduce the cancer risk to an order of magnitude of 1/1000. (See Table 5.)

TABLE 4: ESTIMATED EXCESS LUNG CANCER DEATHS PER 1000 WORKERS FROM OCCUPATIONAL EXPOSURE FROM AGE 20 TO AGE 65, AS PREDICTED BY OSHA'S ALTERNATIVE ANALYSIS*

Exposure Level ($\mu g/m^3$)	Estimates of β (per $\mu g/m^3$-yr)[a]				
	From Mancuso Cohort[b]				From Hayes Cohort
	0.0029	0.0028	0.0024	0.0037	0.00075
0.25	1.7	1.7	1.4	2.2	0.45
0.5	3.5	3.4	2.9	4.4	0.90
1.0	7.0	6.7	5.8	8.9	1.8
2.5	17.0	17.0	14.0	22.0	4.5
5.0	34.0	33.0	28.0	43.0	9.0
52	285	278	246	342	88

[a] β values from linear relative risk model RR = 1+βD employing external controls, where D is cumulative exposure.
[b] The β's from Mancuso Cohort are derived from different treatments of high-exposure groups.
* Table adapted from ICF Kaiser, 1995.

TABLE 5: COMPARISON OF SUPPORTING DATA VS. PROPOSED AND CURRENT PELs

Mancuso Study	JHU Study	Proposed OSHA PEL	Current OSHA PEL
0.08 $\mu g/m^3$	0.275 $\mu g/m^3$	0.5 - 5 $\mu g/m^3$	100 $\mu g/m^3$

Assessment of Quality of Science in Data Sets

The chromium(VI) mortality rates for the Johns Hopkins University study of chromate production workers at a Baltimore, MD plant have been calculated. Drs. Lees and Gibb have not yet published the results; only abstracts and slide presentations are currently available (Lees *et al.*, 1996; Gibb *et al.*, 1996a and 1996b). Overall, this study has several advantages over the 1975 Mancuso report for dose-response assessment (see Table 6). In the JHU study, the unit cancer risk is calculated on exposure to chromium(VI) alone and not total chromium. There is a lower dose exposure group in the JHU study that was not present in the Mancuso study. Preliminary reports indicate there are still risks demonstrated at low chromium(VI) exposure, even without the confounding effects of smoking (see Figure 2). The JHU study will be able to separate out smoking exposure effects from chromate exposure because smoking data was obtained for the cohort.

TABLE 6: PRELIMINARY COMPARISON OF JOHN HOPKINS UNIVERSITY / EPA MORTALITY STUDY ON CHROMATE PRODUCTION WORKERS WITH THE MANCUSO (1975) STUDY*

	Mancuso Study**	JHU Study
Cohort	332 white males	1205 white males 1152 nonwhite males
Estimated Exposure	1949 industrial hygiene data applied to work histories	1950-1985 industrial hygiene data applied to work histories
Exposure	Total Chromium	Chromium(VI)
# Lung cancer deaths	39	122
PY of Observation	5,853	70,736
Smoking data	None	Yes (57%)

* Adapted from Gibb *et al.*, 1996
** Mancuso, 1975

The JHU cohort includes 2357 workers of whom 122 died of lung cancer (Gibb *et al.*, 1996a). The study covers 70,736 person-years of observation. The Mancuso study (1975) had 332 in the cohort with 39 deaths from lung cancer; the person-years of observation were 5,853. The exposure database for the JHU study is based on 200,000 air monitoring measurements of chromium(VI) made between 1950, the beginning year of entry to the cohort, and 1985, the year the plant closed. These measurements were then applied to the work histories to estimate individual exposure. The Mancuso study took air measurements from one short period of time in 1949 and applied those to the work histories to estimate exposure from 1931 through 1937.

The major difference between the Hopkins study and the Mancuso study is in the exposure estimation. Mancuso used industrial hygiene data from one short period in 1949 and extrapolated this to the entire time period of his study (Boggs, 1994). The Hopkins study has voluminous industrial hygiene data, which allows a matrix to be constructed giving annual average exposures for each job category. This provides a more precise estimation of the exposure of each individual in the cohort. Figure 2 shows a comparison of doses by quartile from the JHU study.

The mortality data that best lent itself to dose-response estimation in the Mancuso study was for total chromium. An estimate of the percentage of total chromium that was hexavalent had to be made in order to estimate a dose-response. In the JHU study, a better estimation of exposure to hexavalent chromium can be made.

The Mancuso study had no information on smoking habits of the workers; the JHU study has information on smoking for 57% of the workforce. Of those in the JHU study for whom smoking

data are available, 73% were reported as current smokers at the date of hire. Comparison with smoking rates for the U.S. population shows that whites in the cohort smoked slightly less than U.S. white males while nonwhites in the cohort smoked more than U.S. nonwhite males.

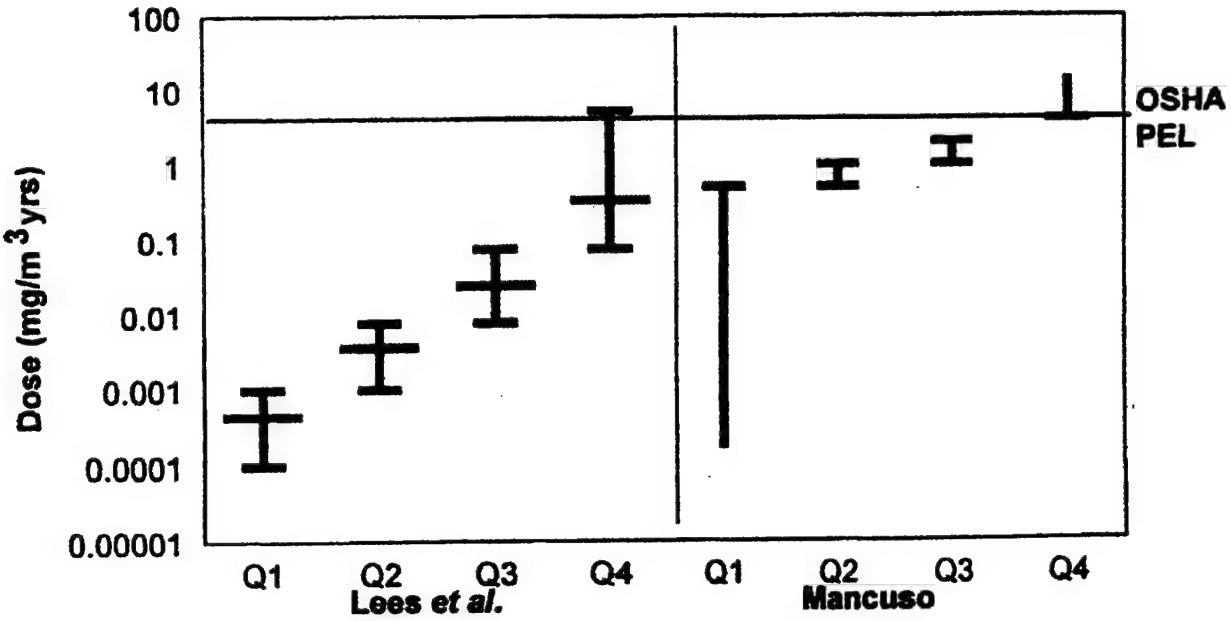

FIGURE 2: COMPARISON OF DOSES BY QUARTILE - LEES *ET AL.* VS. MANCUSO
Adapted from Lees *et al.*, 1996.

UNCERTAINTY ANALYSIS

Sources Leading to Uncertainty Factors

There is a general agreement that hexavalent chromium species are responsible for lung cancer and that the trivalent chromium species is not.

In recent years, several excellent reviews of epidemiological studies of workers exposed to various chromium chemicals have been published (Hayes, 1988; Langard, 1990). There is a critical need for well-designed epidemiological studies incorporating detailed assessments of worker exposures to help elucidate causality, identify specific carcinogenic compounds and quantify risk in humans and eliminating the need to extrapolate from animal data (Lees, 1991).

The lack of worker exposure information is generally the limiting factor in the quantification of risk from epidemiological studies. Even when historic data are available, they are often of limited use because of poor documentation of the sampling and analytical methods employed and limited information on the conditions during sampling. Additionally, exposure samples have generally been collected for purposes other than epidemiology; the reason for sampling dictates the sampling strategy used. Historically, most air sampling in industrial facilities was conducted

in an effort to solve a problem. As such, much historic air sampling may overestimate average exposures (required for epidemiological risk estimation) considerably. Although the need for exposure data crucial to this effort was identified in the earliest epidemiological studies of chromium, such studies have not been conducted. As a result, little more is known today about the relationship between this chemical and disease in humans than was known 40 years ago.

Because of the lack of adequate worker exposure data, epidemiological studies of disease occurrence as a result of chromium exposure are not able to distinguish the risks attributable to the individual compounds, nor are they able to quantify the exposure risk relationship in more than the crudest manner. Despite long-term recognition of these diseases, exposure data have not been generated to help resolve lingering questions of which chromium compounds in what dose cause disease (Lees, 1991).

A major uncertainty in key chromium cancer studies is the lack of speciation data. Therefore the cancer mortality in Mancuso (1975) was assumed to be due to chromium(VI). That was further assumed to be no less than one-seventh of total chromium. The assumption that the ratio of Cr(III) to Cr(VI) is 6:1 may lead to a 7-fold under estimation of risk. OSHA estimated that about 40% of the total chromium in the Mancuso (1975) study was present as hexavalent chromium (ICF Kaiser, 1995).

Further, overestimation of risk may be due to the implicit assumption that the smoking habits of chrome workers were similar to those of the general white male population. OSHA assumed that the smoking habits of chrome workers were similar to those of the U.S. white male population (ICF Kaiser, 1995). The EPA generally accepts that the proportion of smokers is higher for industrial workers than for the general population (IRIS, 1995). Lees indicated there is a higher incidence of smoking among the chromium workers, approaching 75-80%, than in the general population (personal communication, 1996).

Smoking increases epithelial cell proliferation in the respiratory system which is one major factor that differentiates the smoking miner or chromate worker from a nonsmoking member of the general population. Smoking increases epithelial cell proliferation in the mucosa of the larger bronchi. These cells are the targets for cancer development from chromium. It is well established that cell proliferation is an essential factor in the carcinogenic process (Albert, 1991). A characteristic feature of cancer-promoting agents is their ability to increase the level of cell proliferation (Slaga, 1984).

Chronic inhalation of cigarette smoke, in common with other irritants, causes the respiratory mucosa to change from its normal, relatively nonproliferative secretory and ciliated pattern to one of squamous metaplasia, which has a higher than normal proliferation rate (Wehner, 1983). The normally heavy atmospheric loading of irritating dusts, gases and fumes in chromate plants would be expected to cause squamous metaplasia even in the absence of cigarette smoking. Hence, a possibly important difference between the cigarette-smoking chromate worker and the nonsmoker would be the higher proliferation rate in the bronchial mucosa. Cell proliferation may explain how smoking may exacerbate the effects of chromium and lung cancer.

Current Weight-Of-Evidence

The EPA classified chromium(VI) as a Class A (human carcinogen) based on results of occupational epidemiological studies of chromium-exposed workers because the studies are consistent across worker and study populations. Also, dose-response relationships have been established for chromium exposure and lung cancer (IRIS, 1995). Chromium-exposed workers encounter both trivalent and hexavalent forms in different proportions. Because only chromium(VI) has been found to be carcinogenic in animal studies, only chromium(VI) was classified as a human carcinogen.

Overall, the JHU study is more accurate and represents a stronger weight-of-evidence for the existence of cancer at lower doses of chromium(VI) because more people were studied in the JHU study, the exposure was for chromium(VI) alone and the effects of smoking have been controlled. Organization Resources Counselors, Inc. believes that the appropriate use of data from the JHU study, which is expected to be the most accurate and complete database on chromium exposure and mortality available, will permit a much more valid estimation of the respiratory cancer risk due to chromium. Its use will significantly increase the credibility of OSHA's rule making efforts on hexavalent chromium (Boggs, 1994).

Preliminary results of the JHU study indicate a cumulative chromium(VI) exposure is related to risk of lung cancer at a lower exposure concentration than the Mancuso study (Lees *et al.*, 1996).

DATA GAPS AND RECOMMENDATIONS

Data Gaps and Research Needs

1.0 There is a need for well-designed epidemiological studies incorporating detailed assessments of worker exposures to help elucidate causality (Lees, 1991). There is a need for epidemiological studies designed to determine risk from environmental exposures, common exposure to organics and metals, exposure to multiple metals and exposure to carcinogenic metals during adverse dietary conditions including trace element deficiencies (Waalkes *et al.*, 1992).

A special problem in the study of metals is that mixed exposures to more than one metal and to different valences or oxidation states are frequent; precise specifications of individual components of the ambient pollution may not be available because of limitations in the analytical method. Changes in the work process and in the consequent exposure patterns may also have occurred over time without being recognized (Workgroup chaired by Sir Richard Doll, 1981).

1.1 Gibb emphasized the need for chronic exposure studies at higher doses of chromium(III) (personal communication, 1996). Further rodent studies should include dose-response analysis, analysis of carcinogenic potential by relevant routes, analysis of metals as initiators or promoters in defined systems and analysis of multiple metal exposures using combinations that could potentially occur in real world exposure situations (Waalkes *et al.*, 1992).

1.2 There is a need to sort out the effect of confounding variables, such as smoking, from the effects of the chromium (Albert, 1991; Workgroup chaired by Sir Richard Doll, 1981). This point is critical to identify etiologic agent(s) that cause cancer in smokers who are exposed to chromium. The JHU study separated smoking effects from chromium(VI) effects; they found that chromium(VI) still causes cancer, even without smoking. Smoking increases the risk of developing cancer by five to six fold when exposed to chromium (Gibb, personal communication, 1996).

2.0 Mechanisms by which metals exert their carcinogenic effect is enigmatic (Magos, 1991) for the following reasons:

2.1 Different *in vitro* evaluation systems (e.g., bacterial cells versus mammalian cells) frequently give contradictory results (Baker, 1984),

2.2 Many experimental conditions (e.g., intramuscular administration and huge single doses) are not suitable for the identification of crucial steps in a multistage process (Magos, l991), and

2.3 There is no universal mechanism among the metals (Magos, 1991).

3.0 Binding of metal to DNA may cause cancer, but the mechanisms are indeterminate.

It is important to understand the mechanism of chromium carcinogenicity (Gochfeld, 1991b). There are still gaps in understanding of the interactions between hexavalent chromium and DNA on the one hand and the development of cancer on the other (Gochfeld and Witmer, 1991). It is important to understand the mechanisms by which the different chromium species exert toxic effects and the conditions under which these effects are manifest (Gochfeld, 1991b).

There is some discrepancy in the literature as to whether chromium(III) is carcinogenic in humans compared to chromium(VI). The ATSDR Toxicological Profile for Chromium (1993) indicates chromium(III) is carcinogenic by the inhalation route in humans and by the oral route in animals. Some investigators question whether chromium(III) is, in fact, carcinogenic (Lees, 1991; Baruthio, 1992; Paustenbach *et al.*, 1991). However, Magos (1991) indicated that "though exposure to sparingly soluble chromates has the carcinogenic potential, both the kinetics of chromates and the reaction of chromium(III) with DNA indicate that the ultimate carcinogenic species is most likely chromium(VI)". The possibility that the trivalent chromium forms may be the ultimate intracellular carcinogens does not negate the evidence that it is exposure to the hexavalent forms which are predominantly associated with carcinogenesis (Hayes, 1979b).

It has been suggested that, from deposits in the body, small amounts of chromium(III) may be oxidized to the hexavalent state, subsequently causing cancer (Hayes, 1979a). Hayes suggested that this hypothesis has not been widely accepted, yet he indicated it deserves further consideration and clarification because of its potential etiologic importance.

4.0 There is a paucity of information concerning the potential adverse health effects of exposure to hazardous materials for a general population exposed to hazardous materials (Burg and Gist, 1995). Other unknowns include the following:

4.1 Exposure and Bioavailability: What factors govern the movement of chromium from the environment into the body? What influences the bioavailability of chromium from the different routes of exposure (Gochfeld and Witmer, 1991)?

4.2 Biomonitoring: What reliable indicators or markers can be developed to assess exposure and body burden of chromium compounds (Gochfeld and Witmer, 1991)? Alternative means of estimating chromium exposure, such as the development of biomarkers, are an attractive research direction, particularly for a substance which is genotoxic, such as chromium (Gochfeld and Witmer, 1991).

4.3 Pharmacokinetics: How is chromium distributed within the body and what transformations take place that influence its toxicity, storage and excretion (Gochfeld and Witmer, 1991)?

4.4 Toxicity: What can be done to better understand the cellular and subcellular mechanisms by which chromium exerts pathophysiologic, cytotoxic and carcinogenic properties? How do extracellular and intracellular binding and redox reactions differ? What role do antioxidants and other ligands play in influencing toxicity? It is desirable to improve the applicability of animal models for chromium toxicity and carcinogenicity (Gochfeld and Witmer, 1991)?

4.5 Epidemiology: What can be done to improve understanding of the outcome of exposure to chromium compounds in human populations? What can be learned about the toxicity and carcinogenicity of chromium through routes other than inhalation? What evidence is there that risks from chromium are decreasing or increasing in certain settings (Gochfeld and Witmer, 1991; Gochfeld, 1991b)?

4.6 Risk Assessment: For both cancer and noncancer endpoints, how can existing and future data on exposure and health effects be assembled to improve understanding of risk to human populations? What can be done to better deal with the uncertainties implicit in both the toxicologic and epidemiological databases? What are the most reasonable assumptions to be incorporated into the risk assessment (Gochfeld and Witmer, 1991)?

5.0 There is a need to assess the impact of dermal exposure and dermal absorption of chromium. Gochfeld (1991b) reported that "If dermal responsiveness to chromium is widespread, it (rather than cancer) may prove to be the health effect that drives policy regarding mitigation and reduction of exposure." On the other hand, Paustenbach *et al.* (1992) reported that "if one protects against the cancer hazard, the allergic contact dermatitis hazard due to chromium(VI) should be negligible". From these two studies, it appears there is a discrepancy on exposure that causes the adverse effects.

From the above data gaps, it is apparent that research needs span a number of different areas including basic mechanistic biomedical investigations, descriptive studies and experimental approaches in an applied setting (Gochfeld and Witmer, 1991).

Recommendations

1.0 Due to the potential of changes in the criteria for environmental exposure based upon the upcoming release of epidemiology data, the DoD may wish to determine tissue level doses from the dermal and ingestion exposure routes for comparison to the dose from the occupational

inhalation exposures. The biological fate of the initial exposed entity may not represent the toxic entity. DoD waste site managers should be advised of the potential changes to the criteria used to establish clean-up goals due to the potential reassessment of chromium risks.

2.0 Speciation for chromium valence state may be too expensive for routine site characterization for waste sites. Determination of the soil pH and redox potential may be advisable to allow site specific characterization for chromium risk. If the potential risk warrants, then speciation can be performed.

3.0 Increased literature search into the mechanisms of cellular response for the carcinogenic mechanisms may be warranted to provide a testable hypothesis for the ongoing epidemiology studies. Identification of existing kinetic models to assess pharmacological dose is needed. Differentiation between the cancer mechanisms and the micronutrient roles is needed. A critical review of the bioassays used to set the NOAEL levels in conjunction with the assessment of alternative data sets seems warranted due to the uncertainty identified in the current hazard assessments.

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APPENDIX:
EXTRACT OF ATSDR DOSE RESPONSE INFORMATION

TABLE A-1: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - INHALATION*

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL ($mg\ Cr/m^3$)	LOAEL (effect) Less serious ($mg\ Cr/m^3$)	LOAEL (effect) Serious ($mg\ Cr/m^3$)	Reference	Form
ACUTE EXPOSURE								
Death								
1	Rat	4 hr				87 (LC_{50} - F) 137 (LC_{50} - M)	American Chrome and Chemicals 1989	CrO_3 (VI)
2	Rat	4 hr				33 (LC_{50})	Gad et al. 1986	Na_2CrO_4 (VI)
3	Rat	4 hr				31 (LC_{50} - F) 70 (LC_{50} - M)	Gad et al. 1986	$Na_2Cr_2O_7 \cdot 2H_2O$ (VI)
4	Rat	4 hr				45 (LC_{50} - F) 82 (LC_{50} - M)	Gad et al. 1986	$(NH_4)_2Cr_2O_7$ (VI)
5	Rat	4 hr				29 (LC_{50} - F) 35 (LC_{50} - M)	Gad et al. 1986	$K_2Cr_2O_7$ (VI)
Systemic								
6	Hamster	30 min	Resp		0.9 (increase in acid phosphatase in lung tissue)		Henderson et al. 1979	$CrCl_3$ (III)
INTERMEDIATE EXPOSURE								
Systemic								
7	Human	0.2-23.6 yr (2.5 yr[b] avg) (occup)[b]	Resp	0.001[c]	0.002 (nasal mucosa atrophy, mild decreased lung function)		Lindberg and Hedenstierna 1983	CrO_3 (VI)
8	Human	0.5-12 mo (6 mo avg) (occup)[b]	Resp		0.09 (epistaxis, rhinorrhea, ulceration of nasal septum)		Kleinfeld and Rosso 1965	CrO_3 (VI)
9	Human	<1 yr (occup)[b]	Resp		0.1 (epistaxis, rhinorrhea, nasal ulceration and perforation)		Gomes 1972	CrO_3 (VI)

* Excerpted from ATSDR, 1993.

TABLE A-1: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - INHALATION*

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg Cr/m^3)	LOAEL (effect) Less serious (mg Cr/m^3)	LOAEL (effect) Serious (mg Cr/m^3)	Reference	Form
10	Rat	30-90 d 7 d/wk 22 hr/d	Resp		0.05 (increased lung weight, hyperplasia, macrophage infiltration)		Glaser et al. 1990	$Na_2Cr_2O_7 \cdot 2H_2O$ (VI)
			Gastro	0.4				
			Hemato		0.05 (increased white blood cell count)			
			Hepatic	0.4				
			Renal	0.4				
			Other	0.1	0.2 (28% decreased body weight gain)			
11	Rat	90 d 7 d/wk 22 hr/d	Resp	0.1	0.2 (decreased macrophage activity and lung clearance, increased lung weight)		Glaser et al. 1985	$Na_2Cr_2O_7 \cdot 2H_2O$ (VI)
			Gastro	0.2				
			Hemato	0.2				
			Hepatic	0.1	0.2 (increased serum phospholipids and triglycerides)			
			Renal	0.2				
12	Rabbit	4-6 wk 5 d/wk 6 hr/d	Resp		0.6 (decreased macrophage activity; impaired lung function)		Johansson et al. 1986a, 1986b	$Cr(NO_3)_3 \cdot 9H_2O$(III)
13	Rabbit	4-6 wk 5 d/wk 6 hr/d	Resp	0.9			Johansson et al. 1986a, 1986b	Na_2CrO_4 (VI)
14	Mouse	12 mo 2 d/wk 30 min/d	Resp			3.63 (emphysema, nasal septum perforation)	Adachi et al. 1986	CrO_3 (VI)
15	Mouse	12 mo 2 d/wk 120 min/d	Resp			1.81 (emphysema, nasal septum perforation)	Adachi 1987	CrO_3 (VI)

* Excerpted from ATSDR, 1993.

TABLE A-1: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - INHALATION*

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL $_3$ (mg Cr/m^3)	LOAEL (effect) Less serious (mg Cr/m^3)	LOAEL (effect) Serious $_3$ (mg Cr/m^3)	Reference	Form
Immunological								
16	Rat	28 d 7 d/wk 22 hr/d			0.025 (increased response to sheep red blood cells; increased percentage of lymphocytes in bronchoalveolar lavage fluid)		Glaser et al. 1985	$Na_2Cr_2O_7 \cdot 2H_2O$ (VI)
17	Rat	90 d 7 d/wk 22 hr/d			0.025 (increased response to sheep red blood cells; increased percentage of lymphocytes in bronchoalveolar or lavage fluids, increased percentage or macrophages in telophase, increased activity of macrophages)		Glaser et al. 1985	$Na_2Cr_2O_7 \cdot 2H_2O$ (VI)
CHRONIC EXPOSURE								
Systemic								
18	Human	2-12 yr (occup)[b]	Renal	0.075			Foa et al. 1988	Cr_2O_3 (III)
19	Human	3-16 yr (7.5 yr avg) (occup)[b]	Resp		0.004 (epistaxis, rhinorrhea, nasal septum ulceration and perforation)		Lucas and Kramkowski 1975	CrO_3 (VI)
			Gastro		0.004 (stomach pains and cramps, ulcers)			
20	Human	0.1-26 yr (5.3 yr avg) (occup)[b]	Renal		0.004 (increased urinary β_2-microglobulin)		Lindberg and Vesterberg 1983b	CrO_3 (VI)

* Excerpted from ATSDR, 1993.

TABLE A-1: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - INHALATION*

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg Cr/m^3)	LOAEL (effect) Less serious (mg Cr/m^3)	LOAEL (effect) Serious (mg Cr/m^3)	Reference	Form
21	Human	0.2-23.6 yr (2.5 yr avg) (occup)[b]	Resp	0.001[c]	0.002 (nasal mucosa atrophy, mild decreased lung function)		Lindberg and Hedenstierna 1983	CrO_3 (VI)
22	Human	11-19 yr (occup)[b]	Gastro		0.005 (gastric mucosa irritation, ulcers)		Sterechova et al. 1978	CrO_3 (VI)
23	Human	1-32 yr (7 yr avg) (occup)[b]	Renal	0.61			Triebig et al. 1987	Chromium (0)
24	Human	2.3-12.6 yr (6.9 yr avg) (occup)[b]	Resp		0.414 (nasal septum perforation)		Hanslian et al. 1967	CrO_3 (VI)
			Gastro		0.414 (chronic tonsillitis, chronic pharyngitis, atrophy of larynx)			
25	Human	7 yr avg (occup)[b]	Renal		0.05 (increase in retinal binding protein and tubular antigens in urine)		Franchini and Mutti 1988	CrO_3 (VI)
26	Human	(occup)[b]	Resp	1.99			Korallus et al. 1974a	Cr_2O_3 and $Cr_2(SO_4)_3$ (III)
			Hemato	1.99				
27	Rat	18 mo 7 d/wk 22 hr/d	Resp	0.1			Glaser et al. 1986, 1988	$Na_2Cr_2O_7 \cdot 2H_2O$ (VI)
			Hemato	0.1				
			Hepatic	0.1				
			Renal	0.1				
28	Rat	2 yr 5 d/wk 6 hr/d	Resp	15.5			Lee et al. 1989	CrO_2 (IV)
			Cardio	15.5				
			Gastro	15.5				
			Hemato	15.5				
			Hepatic	15.5				
			Renal	15.5				
			Derm/oc	15.5				

* Excerpted from ATSDR, 1993.

TABLE A-1: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - INHALATION*

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL ($mg\ Cr/m^3$)	LOAEL (effect) Less serious ($mg\ Cr/m^3$)	LOAEL (effect) Serious ($mg\ Cr/m^3$)	Reference	Form
29	Rat	18 mo 7 d/wk 22 hr/d	Resp			0.1 (interstitial fibrosis of lung)	Glaser et al. 1986, 1988	CrO_3 and Cr_2O_3 (VI + III)
			Hemato		0.1 (increased RBC, WBC)			
			Hepatic	0.1				
			Renal	0.1				
30	Rat	2 yr 4 d/wk 4-5 hr/d	Resp			1.6 (granulomata, giant cells, broncho-pneumonia, abscesses)	Steffee and Baetjer 1965	Finely ground chromium roast (VI)
31	Gn pig	4.5 yr	Resp			1.6 (alveolar and interstitial inflammation; alveolar hyperplasia; interstitial fibrosis)	Steffee and Baetjer 1965	Mixed chromium roast $K_2Cr_2O_7$, Na_2CrO_4 (VI)
32	Mouse	18 mo 5 d/wk 5.5 hr/d	Resp			4.3 (epithelial necrosis, hyperplasia)	Nettesheim and Szakal 1972	$CaCrO_4$ (VI)
Cancer								
33	Human	1-7 yr (occup)[b]				0.25 (CEL: lung)	Mancuso 1975	soluble Cr(VI)
34	Human	1-7 yr (occup)[b]				0.25 (CEL: lung)	Mancuso 1975	insoluble Cr(III)
35	Human	1-49 yr (occup)[b]				0.04 (CEL: lung)	Langard et al. 1980	mix of (VI) and (III)
36	Human	4-19 yr (occup)[b]				0.5 (CEL: lung)	Langard and Norseth 1975	$PbCrO_4$ and $ZnCrO_4$ (VI)
37	Human	≥10 yr (occup)[b]				0.5 (CEL: lung)	Hayes et al. 1989	$PbCrO_4$ and $ZnCrO_4$ (VI)

* Excerpted from ATSDR, 1993.

TABLE A-1: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - INHALATION*

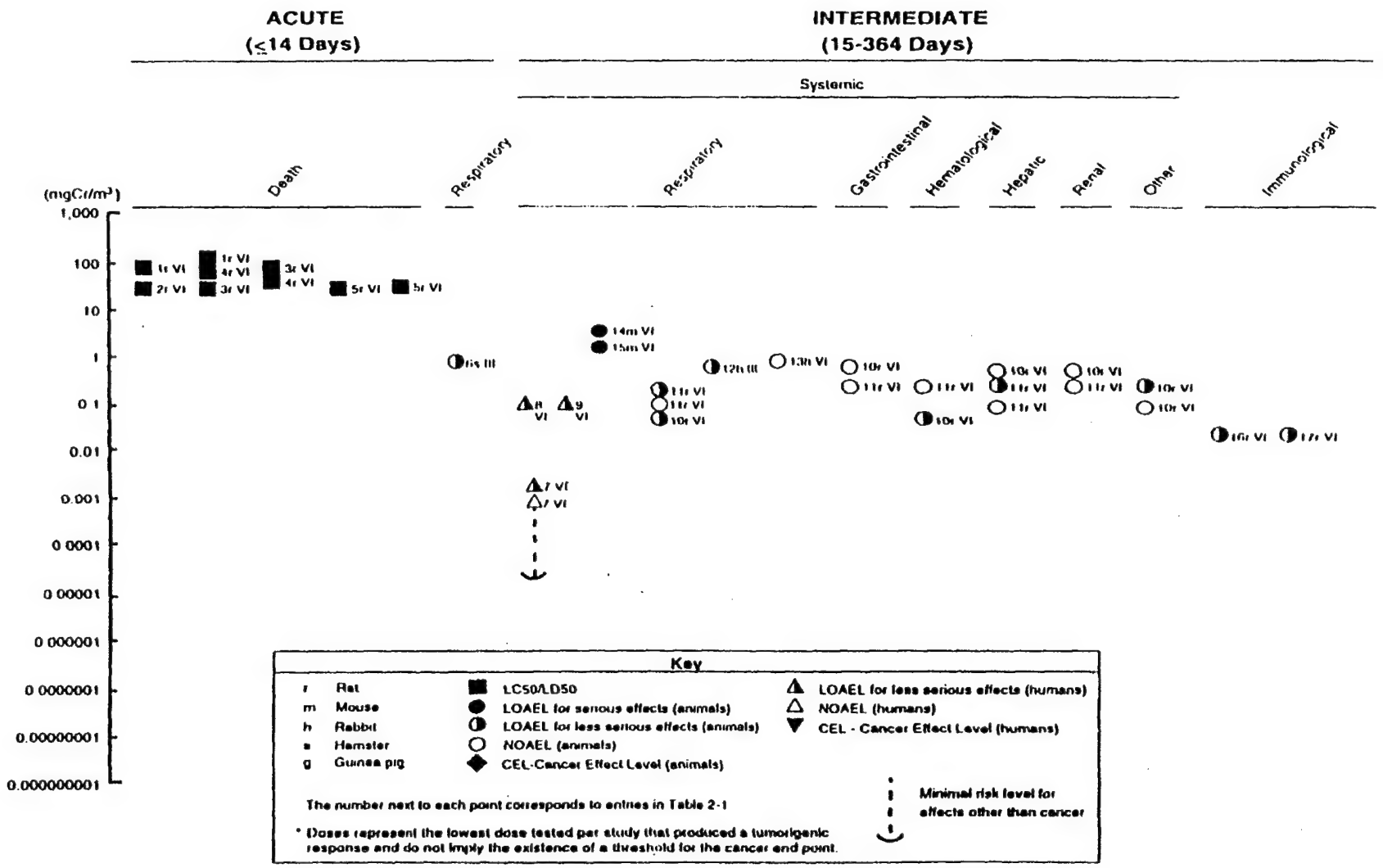
Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (mg Cr/m^3)	LOAEL (effect) Less serious (mg Cr/m^3)	LOAEL (effect) Serious (mg Cr/m^3)	Reference	Form
38	Human	1 mo-29 yr (occup)[b]				0.1 (CEL: lung)	Sheffet et al. 1982	$PbCrO_4$ and $ZnCrO_4$ (VI)
39	Human	1-7 yr (occup)[b]				0.5 (CEL: lung)	Mancuso 1975	mix of (VI) and (III)
40	Human	90 d->5 yr (occup)[b]				0.413 (CEL: lung)	Braver et al. 1985; Hayes et al. 1979	mix of (VI) and (III)
41	Rat	18 mo 7 d/wk 22 hr/d				0.1 (CEL: lung)	Glaser et al. 1986, 1988	$Na_2Cr_2O_7 \cdot 2H_2O$ (VI)
42	Mouse	18 mo 5 d/wk 5 hr/d				4.3 (CEL: lung)	Nettesheim et al. 1971	$CaCrO_4$ (VI)

[a]The number corresponds to entries in Figure 2-1.
[b]Occup = occupational exposure = 5 d/wk, 8 hr/d
[c]Used to derive intermediate and chronic inhalation minimal risk level (MRL) of 0.00002 mg chromium(VI)/m^3. Exposure concentration adjusted for intermittent occupational exposure and divided by an uncertainty factor of 10 for human variability.

(0) = 0 valence; (III) = trivalent; (IV) = tetravalent; (VI) = hexavalent; avg = average; $CaCrO_4$ = calcium chromate; Cardio = cardiovascular; CEL = cancer effect level; Cr = chromium; $CrCl_3$ = chromium trichloride; $Cr(NO_3)_3 \cdot 9H_2O$ = chromium nitrate; CrO_2 = chromium dioxide; CrO_3 = chromium trioxide; Cr_2O_3 = chromium oxide; d = day; Derm/oc = dermal/ocular; F = female; Gastro = gastrointestinal; Hemato = hematological; hr = hour; $K_2Cr_2O_7$ = potassium dichromate; LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minutes; mo = months; Na_2CrO_4 = sodium chromate; $Na_2Cr_2O_7 \cdot 2H_2O$ = sodium dichromate dihydrate; $(NH_4)_2Cr_2O_7$ = ammonium dichromate; NOAEL = no-observed-adverse-effect level; (occup) = occupational; $PbCrO_4$ = lead chromate; RBC = red blood cell; Resp = respiratory; WBC = white blood cell; wk = weeks; x = times; yr = years; $ZnCrO_4$ = zinc chromate

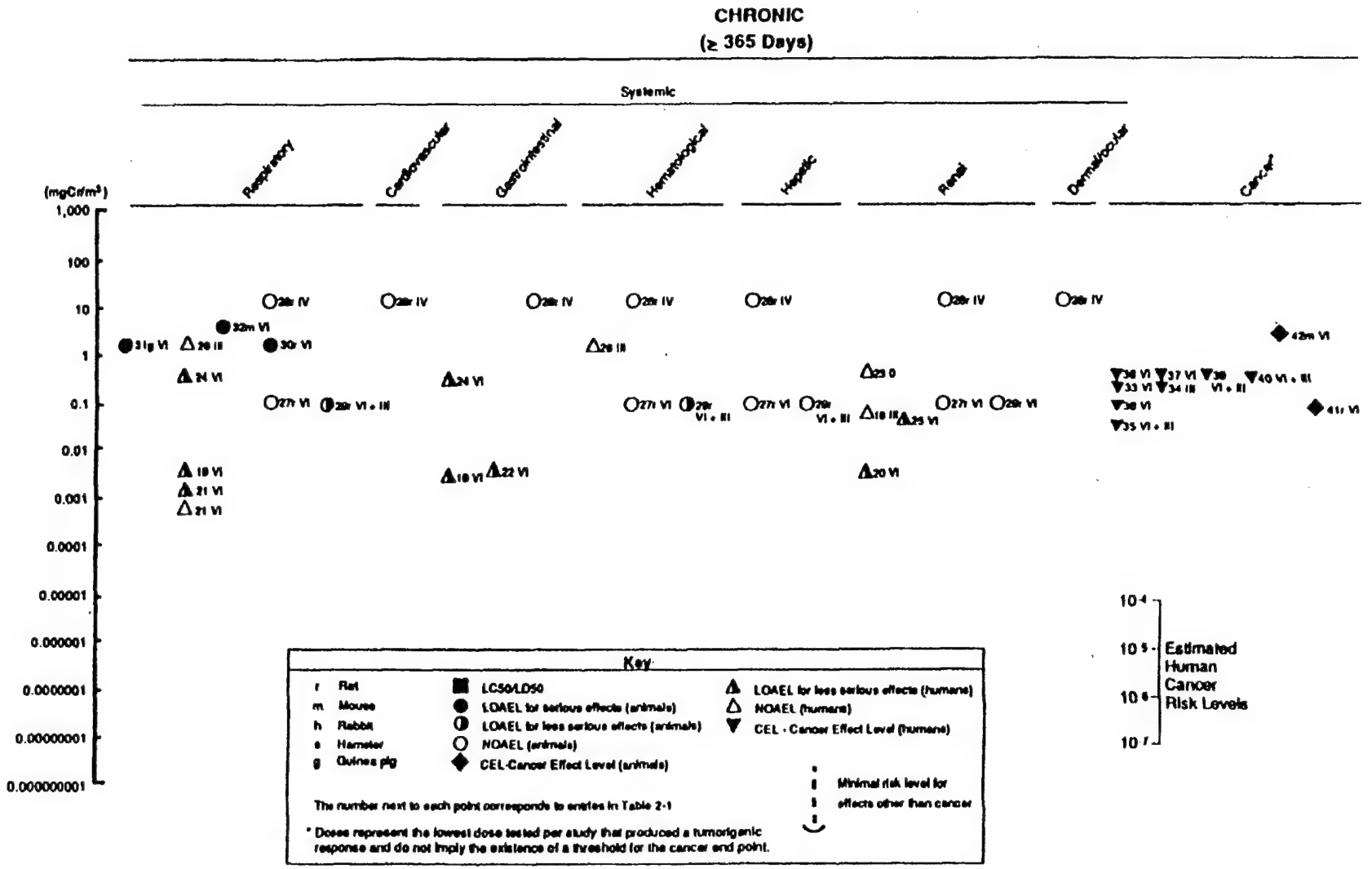
* Excerpted from ATSDR, 1993.

FIGURE A-1: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - INHALATION*



* Excerpted from ATSDR, 1993.

FIGURE A-1: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - INHALATION*



* Excerpted from ATSDR, 1993.

TABLE A-2: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - ORAL*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg Cr/kg/day)	LOAEL (effect) Less serious (mg Cr/kg/day)	LOAEL (effect) Serious (mg Cr/kg/day)	Reference	Form
ACUTE EXPOSURE									
Death									
1	Human	(W)	1 x				4.1[b]	Saryan and Reedy 1988	CrO_3 (VI)
2	Human	(F)	1 x				7.5[c]	Kaufman et al. 1970	$K_2Cr_2O_7$ (VI)
3	Human	(G)	1 x				29[d]	Clochesy 1984; Iserson et al. 1983	$K_2Cr_2O_7$ (VI)
4	Rat	(G)	1 x				183 (LD_{50} - F) 200 (LD_{50} - M)	Vernot et al. 1977	$Cr(NO_3)_3 \cdot 9H_2O$ (III)
5	Rat	(GW)	1 x				14 (LD_{50} - F) 21 (LD_{50} - M)	Gad et al. 1986	$Na_2Cr_2O_7 \cdot 2H_2O$ (VI)
6	Rat	(G)	1 x				25 (LD_{50} - F) 29 (LD_{50} - M)	American Chrome and Chemicals 1989	CrO_3 (VI)
7	Rat	(G)	1 x				108 (LD_{50} - F) 249 (LD_{50} - M)	Vernot et al. 1977	$CaCrO_4$ (VI)
8	Rat	(GW)	1 x				13 (LD_{50} - F) 28 (LD_{50} - M)	Gad et al. 1986	Na_2CrO_4 (VI)
9	Rat	(GW)	1 x				2,365 (LD_{50})	Smyth et al. 1969	$Cr(CH_3COO)_3 \cdot H_2O$ (III)
10	Rat	(GW)	1 x				19 (LD_{50} - F) 22 (LD_{50} - M)	Gad et al. 1986	$(NH_4)_2Cr_2O_7$ (VI)

* Excerpted from ATSDR, 1993.

TABLE A-2: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - ORAL*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg Cr/kg/day)	LOAEL (effect) Less serious (mg Cr/kg/day)	LOAEL (effect) Serious (mg Cr/kg/day)	Reference	Form
11	Rat	(GW)	1 x				17 (LD_{50} - F) 26 (LD_{50} - M)	Gad et al. 1986	$K_2Cr_2O_7$ (VI)
12	Rat	(G)	1 x				811 (LD_{50} - M)	Shubochkin and Pokhodzei 1980	$SrCrO_4$ (VI)
Systemic									
13	Human	(F)	1 x	Gastro		7.5[c] (abdominal pain and vomiting)		Kaufman et al. 1970	$K_2Cr_2O_7$ (VI)
				Hepatic			7.5[c] (increased SGOT and SGPT; marked necrosis seen at autopsy)		
				Renal			7.5[c] (tubular necrosis, edema, anuria)		
14	Human	(G)	1 x	Resp			29[d] (congested lungs pleural effusions)	Clochesy 1984; Iserson et al. 1983	$K_2Cr_2O_7$ (VI)
				Cardio			29[d] (hemorrhage, cardiac arrest)		
				Gastro			29[d] (hemorrhage)		
				Hemato			29[d] (inhibited coagulation)		
				Renal			29[d] (necrosis swelling of renal tubules)		
15	Human	(W)	1 x	Gastro			4.1[b] (gastrointestinal hemorrhage)	Saryan and Reedy 1988	CrO_3 (VI)
				Hemato		4.1[b] (decreased hemoglobin)			
				Renal			4.1[b] (acute tubular necrosis)		
16	Human	(C)	1 x	Derm/oc		0.036 (enhancement of dermatitis)		Kaaber and Veien 1977	$K_2Cr_2O_7$ (VI)

* Excerpted from ATSDR, 1993.

TABLE A-2: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - ORAL*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg Cr/kg/day)	LOAEL (effect) Less serious (mg Cr/kg/day)	LOAEL (effect) Serious (mg Cr/kg/day)	Reference	Form
17	Human	(G)	1 x	Derm/oc		0.04 (enhancement of dermatitis)		Goitre et al. 1982	$K_2Cr_2O_7$ (VI)
18	Rat	(G)	1 x	Gastro			130 (hemorrhage)	Samitz 1970	$K_2Cr_2O_7$ (VI)
Immunological									
19	Human	(G)	1 x			0.04 (enhancement of chromium dermatitis)		Goitre et al. 1982	$K_2Cr_2O_7$ (VI)
20	Human	(C)	1 x			0.036 (enhancement of dermatitis)		Kaaber and Veien 1977	$K_2Cr_2O_7$ (VI)
Neurological									
21	Human	(F)	1 x				7.5[c] (cerebral edema)	Kaufman et al. 1970	$K_2Cr_2O_7$ (VI)
INTERMEDIATE EXPOSURE									
Systemic									
22	Rat	(F)	90 d 5 d/wk	Resp Cardio Gastro Hemato Hepatic Renal	1,806 1,806 1,806 1,806 1,806 1,806			Ivankovic and Preussmann 1975	Cr_2O_3 (III)
23	Rat	(W)	28 d	Renal	9.8		98 (proteinuria, oliguria)	Diaz-Mayans et al. 1986	Na_2CrO_4 (VI)
24	Rat	(G)	20 d 7 d/wk	Hepatic Renal		13.5 (lipid accumulation) 13.5 (lipid accumulation)		Kumar and Rana 1982	K_2CrO_4 (VI)
25	Rat	(G)	20 d 7 d/wk	Renal		13.5 (inhibition of membrane enzymes)		Kumar and Rana 1984	K_2CrO_4 (VI)

* Excerpted from ATSDR, 1993.

TABLE A-2: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - ORAL*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg Cr/kg/day)	LOAEL (effect) Less serious (mg Cr/kg/day)	LOAEL (effect) Serious (mg Cr/kg/day)	Reference	Form
26	Rat	(G)	20 d 7 d/wk	Hepatic		13.5 (changes in liver enzyme activities)		Kumar et al. 1985	K_2CrO_4 (VI)
27	Mouse	(W)	19 d	Other	57	120 (decreased maternal weight gain)		Trivedi et al, 1989	$K_2Cr_2O_7$ (VI)
Immunological									
28	Rat	(W)	3-10 wk			7 (increased proliferation of T- and B-lymphocytes in response to mitogens and antigens)		Snyder and Valle 1991	K_2CrO_4 (VI)
Neurological									
29	Rat	(W)	28 d		9.8	98 (decreased motor activity)		Diaz-Mayans et al. 1986	Na_2CrO_4 (VI)
Developmental									
30	Rat	(F)	90 d 5 d/wk		1,806			Ivankovic and Preussmann 1975	Cr_2O_3 (III)
31	Mouse	(W)	19 d Gd 1-19				57 (increased resorptions, reduced ossification, gross anomalies)	Trivedi et al. 1989	$K_2Cr_2O_7$ (VI)
Reproductive									
32	Rat	(F)	90 d 5 d/wk		1,806			Ivankovic and Preussmann 1975	Cr_2O_3 (III)

* Excerpted from ATSDR, 1993.

TABLE A-2: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - ORAL*

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg Cr/kg/day)	LOAEL (effect) Less serious (mg Cr/kg/day)	LOAEL (effect) Serious (mg Cr/kg/day)	Reference	Form
33	Mouse	(W)	19 d Gd 1-19				57 (increase in fetal resorption and postimplantation loss)	Trivedi et al. 1989	$K_2Cr_2O_7$ (VI)
34	Mouse	(F)	7 wk 7 d/wk				4.6 (decreased spermatogenesis)	Zahid et al. 1990	$K_2Cr_2O_7$ (VI)
35	Mouse	(F)	7 wk 7 d/wk				3.5 (decreased spermatogenesis)	Zahid et al. 1990	$Cr_2(SO_4)_3$ (III)
CHRONIC EXPOSURE									
Systemic									
36	Human	(W)	NR (environmental)	Gastro		0.57 (oral ulcer, diarrhea, abdominal pain, indigestion, vomiting)		Zhang and Li 1987	(VI)
				Hemato		0.57 (leukocytosis, immature neutrophils)			
37	Rat	(W)	1 yr 7 d/wk	Hemato Hepatic Renal	2.7 2.7 2.7			Mackenzie et al. 1958	$CrCl_3$ (III)
38	Rat	(W)	1 yr 7 d/wk	Hemato Hepatic Renal	3.5 3.5 3.5			Mackenzie et al. 1958	K_2CrO_4 (VI)
39	Rat	(W)	2-3 yr 7 d/wk	Cardio Hepatic Renal	0.46 0.46 0.46			Schroeder et al. 1965	$Cr(CH_3COO)_3 \cdot H_2O$ (III)

* Excerpted from ATSDR, 1993.

TABLE A-2: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - ORAL*

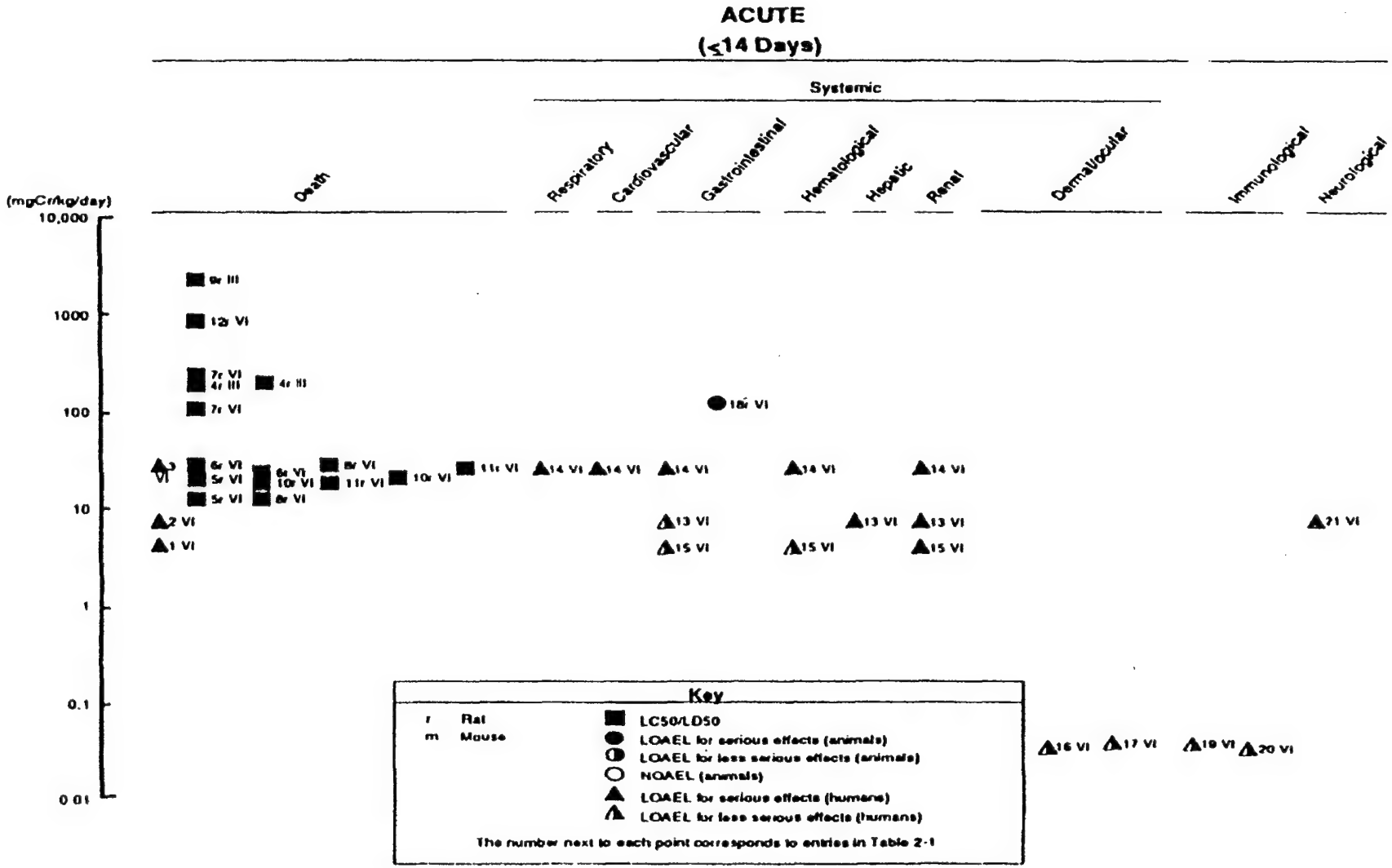
Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg Cr/kg/day)	LOAEL (effect) Less serious (mg Cr/kg/day)	LOAEL (effect) Serious (mg Cr/kg/day)	Reference	Form
40	Rat	(F)	2 yr 5 d/wk	Resp	2,040			Ivankovic and Preussmann 1975	Cr_2O_3 (III)
				Cardio	2,040				
				Gastro	2,040				
				Hepatic	2,040				
				Renal	2,040				

[a]The number corresponds to entries in Figure 2-2.
[b]Case study of 44-year-old man ingesting liquid containing =2.8 g chromium(VI) as chromium trioxide; =4.1 mg chromium(VI)/kg body weight.
[c]Case study of 14-year-old boy who ingested 1.5 g potassium dichromate (0.53 mg chromium[VI]). Since body weight was not reported, the standard 70 kg body weight was used to calculate the dose of 7.5 mg chromium(VI)/kg.
[d]Case study of a 17-year-old, 60 kg boy who ingested 5 g potassium dichromate (1,750 mg chromium[VI]); 1,750 mg/60 kg = 29 mg chromium(VI)/kg.

(III) = trivalent; (VI) = hexavalent; $CaCrO_4$ = calcium chromate; 1 x = one time; (C) = capsule; Cardio = cardiovascular; Cr = chromium; $Cr(CH_3COO)CH_3 \cdot H_2O$ = chromium acetate monohydrate; $CrCl_3$ = chromium trichloride; $Cr(NO_3)_3 \cdot 9H_2O$ = chromium nitrate nonahydrate; CrO_3 = chromium trioxide; Cr_2O_3 = chromium oxide; $Cr_2(SO_4)_3$ = chromium sulfate; d = day(s); Derm/oc = dermal/ocular; (F) = feed; F = female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GW) = gavage in water; Hemato = hematological; K_2CrO_4 = potassium chromate; $K_2Cr_2O_7$ = potassium dichromate; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Na_2CrO_4 = sodium chromate; $Na_2Cr_2O7 \cdot 2H_2O$ = sodium dichromate dihydrate; $(NH_4)_2Cr_2O_7$ = ammonium dichromate; NOAEL = no-observed-adverse-effect level; Resp = respiratory; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; (W) = drinking water; wk = week(s); yr = year(s)

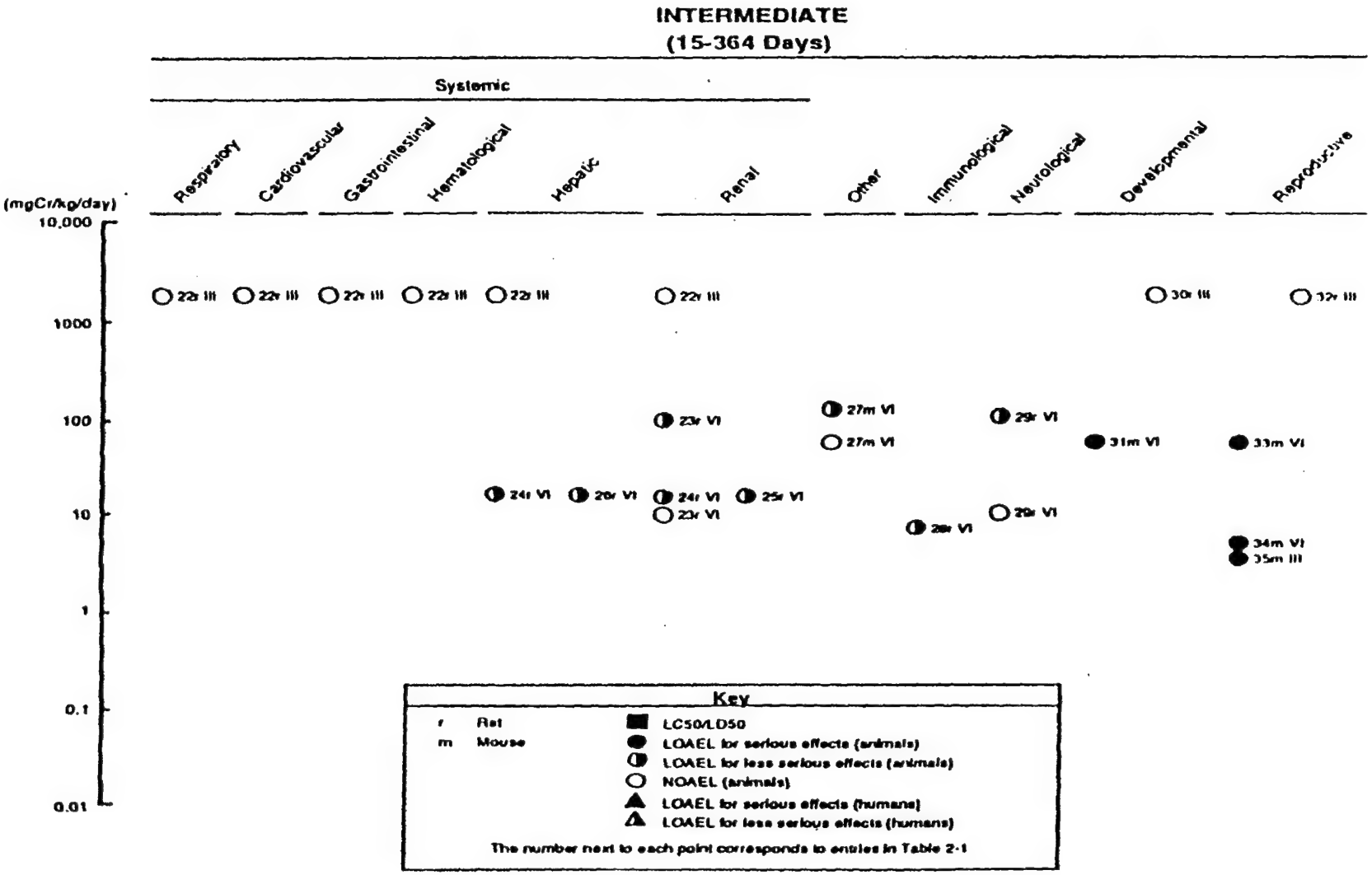
* Excerpted from ATSDR, 1993.

FIGURE A-2: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - ORAL*



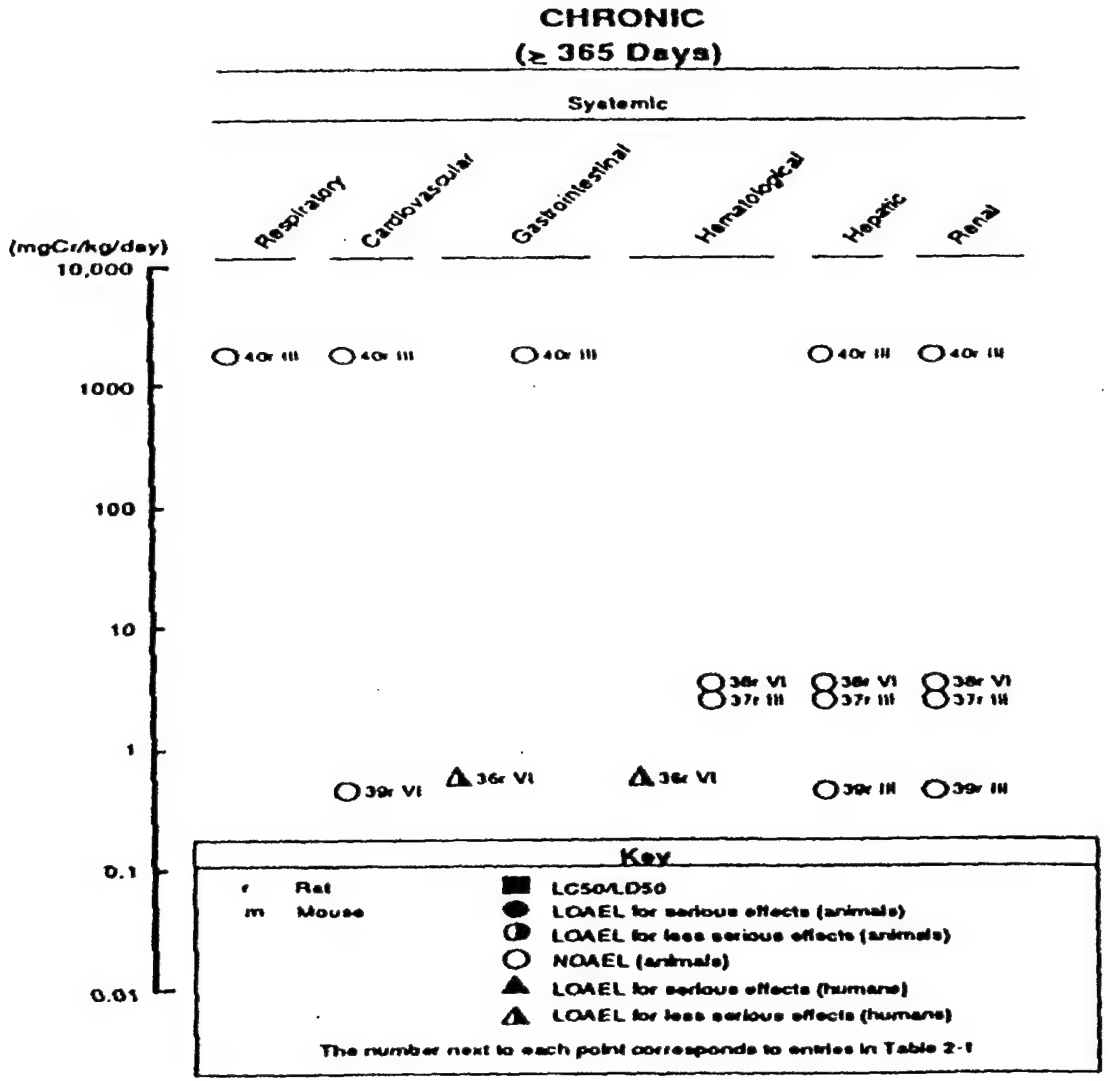
* Excerpted from ATSDR, 1993.

FIGURE A-2: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - ORAL*



* Excerpted from ATSDR, 1993.

FIGURE A-2: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - ORAL*



* Excerpted from ATSDR, 1993.

TABLE A-3: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - DERMAL*

Species	Exposure[a] duration/ frequency	System	NOAEL	LOAEL (effect) Less serious	LOAEL (effect) Serious	Reference	Form
ACUTE EXPOSURE							
Death							
Rabbit	1 d				30 mg/kg (LD_{50})	American Chrome and Chemicals 1989	CrO_3 (VI)
Rabbit	1 d				490 mg/kg (LD_{50} - F) 403 mg/kg (LD_{50} - M)	Gad et al. 1986	$K_2Cr_2O_7$ (VI)
Rabbit	1 d				549 mg/kg (LD_{50} - F) 763 mg/kg (LD_{50} - M)	Gad et al. 1986	$(NH_4)_2Cr_2O_7$ (VI)
Rabbit	1 d				361 mg/kg (LD_{50} - F) 336 mg/kg (LD_{50} - M)	Gad et al. 1986	$Na_2Cr_2O_7 \cdot 2H_2O$ (VI)
Rabbit	2 d				553 mg/kg (LD_{50} - F) 426 mg/kg (LD_{50} - M)	Gad et al. 1986	Na_2CrO_4 (VI)
Systemic							
Rat	1 x	Hepatic		0.175% (altered carbohydrate metabolism)		Merkur'eva et al. 1982	$K_2Cr_2O_7$ (VI)
		Derm/oc		0.175% (dermatitis)			
Rabbit	4 hr	Derm/oc		47 mg/kg (necrosis, skin inflammation, edema)		Gad et al. 1986	$Na_2Cr_2O_7 \cdot 2H_2O$ (VI)
Rabbit	4 hr	Derm/oc		55 mg/kg (necrosis, skin inflammation, edema)		Gad et al. 1986	$(NH_4)_2Cr_2O_7$ (VI)
Rabbit	4 hr	Derm/oc		47 mg/kg (necrosis; skin inflammation, edema)		Gad et al. 1986	$K_2Cr_2O_7$ (VI)
Rabbit	4 hr	Derm/oc		42 mg/kg (necrosis, skin inflammation, necrosis)		Gad et al. 1986	Na_2CrO_4 (VI)

* Excerpted from ATSDR, 1993.

TABLE A-3: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - DERMAL*

Species	Exposure[a] duration/ frequency	System	NOAEL	LOAEL (effect) Less serious	LOAEL (effect) Serious	Reference	Form
Rabbit	5 min or 24 hr	Derm/oc	0.1 mL of 1000 mg/L			Fujii et al. 1976	Na_2CrO_4 and $Na_2Cr_2O_7$ (VI)
Gn pig	1 d	Derm/oc		1.9 mg/kg (skin ulcers)		Samitz 1970	$K_2Cr_2O_7$ (VI)
Gn pig	3 d 1 x/d	Derm/oc	1 mg/kg			Samitz and Epstein 1962	$Cr_2(SO_4)_3$ (III)
Gn pig	3 d 1 x/d	Derm/oc		0.35 mg/kg (skin ulcers)		Samitz and Epstein 1962	$K_2Cr_2O_7$ (VI)
Immunological							
Human	48 hr			0.175% (positive patch test, chromium allergy)		Peltonen and Fraki 1983	$K_2Cr_2O_7$ (VI)
Human	48 hr			0.09% (positive patch test)		Wahba and Cohen 1979	$K_2Cr_2O_7$ (VI)
Human	48 hr			0.001% (increased skin thickness and blood flow)		Eun and Marks 1990	$K_2Cr_2O_7$ (VI)
Human	48 hr			0.33 mg (positive patch test, skin inflammation)		Samitz and Shrager 1966	$Cr_2(SO_4)_3$ (III)
Human	48 hr			0.26% (positive patch test, skin inflammation)		Levin et al. 1959	CrO_3 (VI)
Human	48 hr			0.09 mg (positive patch test, skin inflammation)		Samitz and Shrager 1966	$K_2Cr_2O_7$ (VI)
Human	48 hr			0.175% (positive patch test)		Newhouse 1965	$K_2Cr_2O_7$ (VI)

* Excerpted from ATSDR, 1993.

TABLE A-3: LEVELS OF SIGNIFICANT EXPOSURE TO CHROMIUM - DERMAL*

Species	Exposure[a] duration/ frequency	System	NOAEL	LOAEL (effect) Less serious	LOAEL (effect) Serious	Reference	Form
Human	12–48 hr			0.16 $\mu g/mm^2$ (positive patch test)		Mali et al. 1966	$CrCl_3$ (III)
Human	48 hr			0.16 mg (positive patch test inflammation)		Samitz and Shrager 1966	$Cr(NO_3)_3$ (III)
Human	48 hr			0.08 mg (positive patch test, skin inflammation)		Samitz and Shrager 1966	$CrCl_3$ (III)
Human	48 hr			0.175% (positive patch test)		Engelbrigsten 1952	$K_2Cr_2O_7$ (VI)
Human	48 hr			0.37% (positive patch test)		Fregert and Rorsman 1964	$CrCl_3 \cdot 6H_2O$ (III)
Human	12–48 hr		0.0013 $\mu g/mm^2$	0.0026 $\mu g/mm^2$ (positive patch test)		Mali et al. 1966	$K_2Cr_2O_7$ (VI)
Human	48 hr			0.09% (positive patch test)		Winston and Walsh 1951	$Na_2Cr_2O_7$ (VI)
Gn pig	1 d			0.009 mg/kg (contact sensitivity)		Gross et al. 1968	$K_2Cr_2O_7$ (VI)
Gn pig	1 d			0.03 mg/kg (skin inflammation after sensitization)		Jansen and Berrens 1968	$Cr_2(SO_4)_3$ (III)
Gn pig	1 d			0.004 mg/kg (erythematic reaction after sensitization)		Gross et al. 1968	$CrCl_3$ (III)
Gn pig	1 d			0.04 mg/kg (skin inflammation after sensitization)		Jansen and Berrens 1968	$K_2Cr_2O_7$ (VI)

[a]All exposures are expressed in terms of Chromium.

(III) = trivalent; (VI) = hexavalent; 1 x = one time; $CrCl_3$ = chromium trichloride; CrO_3 = chromium trioxide; $Cr_2(SO_4)_3$ = chromium sulfate; d = day(s); Derm/oc = dermal/ocular; F = female; Gn pig = guinea pig; hr = hour(s); K_2CrO_4 = potassium chromate; $K_2Cr_2O_7$ = potassium dichromate; kg = kilogram; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mg = milligrams; Na_2CrO_4 = sodium chromate; $Na_2Cr_2O_7 \cdot 2H_2O$ = sodium dichromate dihydrate; $(NH_4)_2Cr_2O_7$ = ammonium dichromate; NOAEL = no-observed-adverse-effect level

* Excerpted from ATSDR, 1993.

FIGURE A-3: EXISTING INFORMATION ON HEALTH EFFECTS OF CHROMIUM(III)*

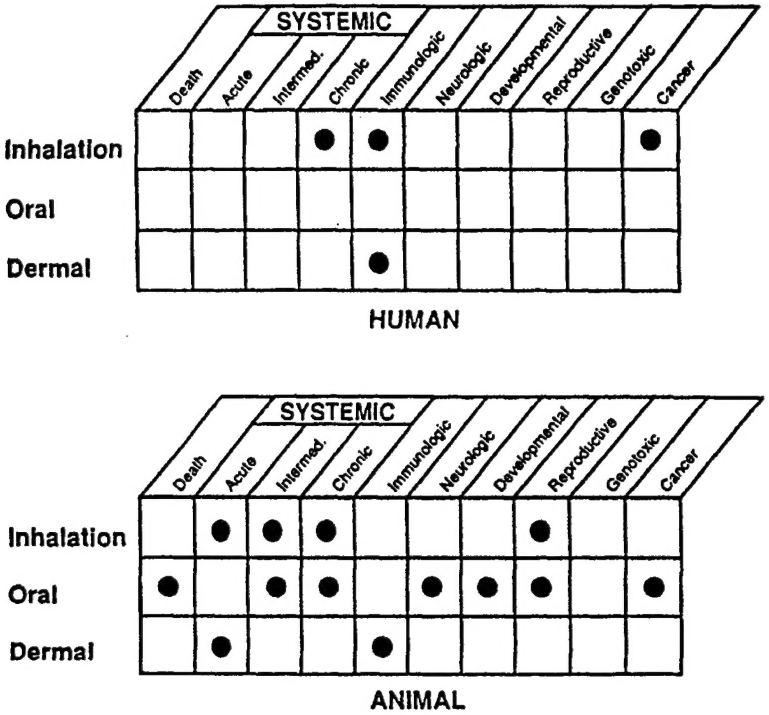
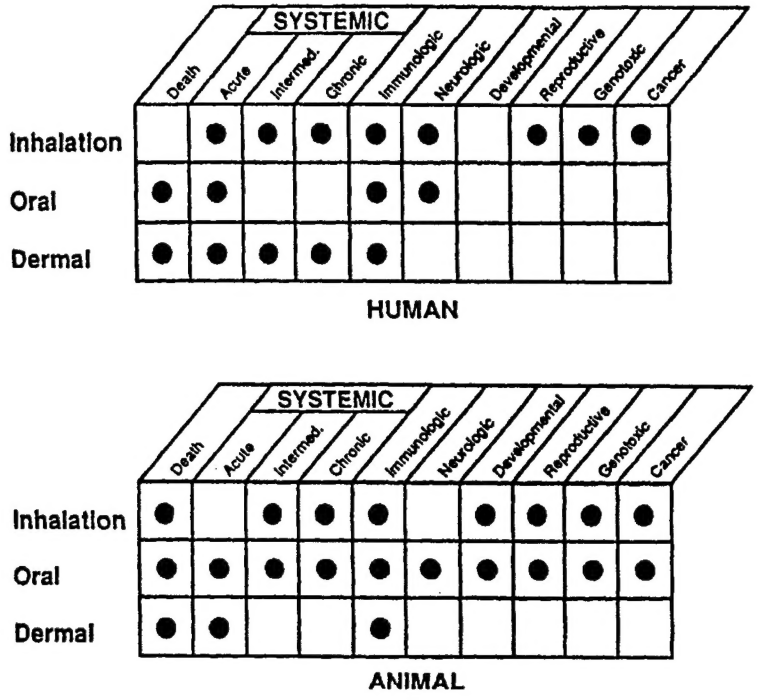


FIGURE A-4: EXISTING INFORMATION HEALTH EFFECTS OF CHROMIUM(VI)*



* Excerpted from ATSDR, 1993.